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Bibliography: 1. Clinical reports on file, Roche Laboratories. 2. W. Hollander and R. W. Wilkins in J. H. Moyer, Ed., *Hypertension*, Philadelphia, W. B. Saunders Co., 1959, p. 399. 3. R. W. Oblath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. 4. I. Kimbell, paper read at Cooperative Chemotherapy Studies in Psychiatry, 4th Annual Research Conference, Memphis, Tenn., May 20-22, 1959.

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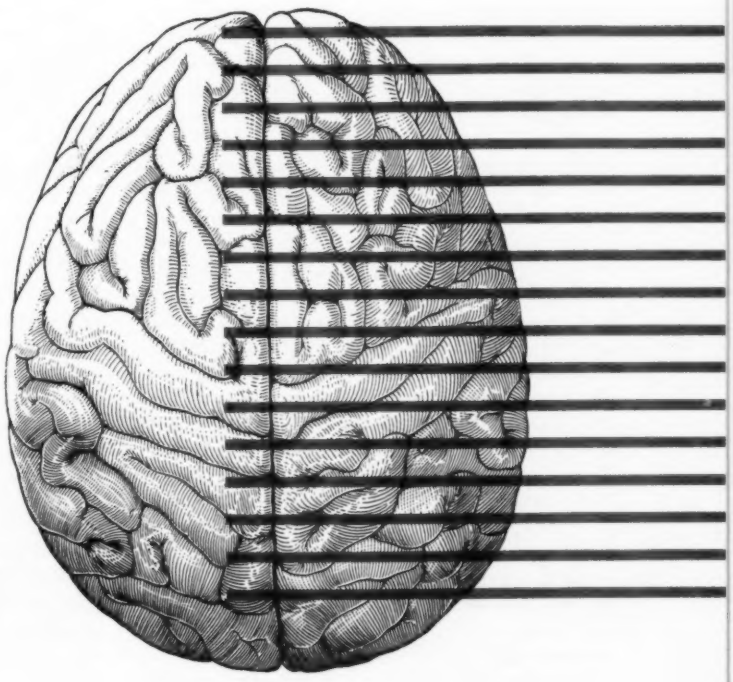


Your Questions answered

Readers may send questions from their own practice or other medical problems which will be answered by qualified consultants. Replies are forwarded by mail immediately and selected questions and answers are published each month in this section.

• HYALINE DISEASE OF THE NEWBORN

Q. I recently examined a 23 year old woman, Gravida V Para IV, who was seven and one-half months pregnant. Labor was normal in the birth of her first two children; however, in her next two pregnancies she went into spontaneous labor at eight months. In each case the infant, who appeared to be healthy, died 20 to 40 minutes after delivery.

The patient's past history was noncontributory, and her family physician had earlier done numerous blood studies to rule out other illness. When I examined her, she was emotionally upset and was deteriorating physically with anorexia and loss of weight; however, there were no other abnormal findings and the heart beat and position of the fetus seemed normal.

In her last two pregnancies the patient had begun to feel ill about a month before the onset of premature labor. When I saw her she had been ill for two or three weeks. Part of this illness was emotional in origin; however, could it have been merely a coincidence that she had had a similar illness before the first premature birth?

After consultation with other physicians, I induced labor by rupturing the membranes and by use of PITOCIN® drip one week before the eighth month of pregnancy. Premedication consisted of 25 mg. promazine given intramuscularly. A 3 lb. 10 oz. infant was born in less than two hours. The baby cried instantaneously and appeared healthy in all respects. Because of the past history, he was placed in an atmosphere of moist oxygen. Respiratory distress began one hour later and the infant died 15 hours after delivery. The postmortem diagnosis was hyaline disease.

Assuming that this disease also had caused the death of the other two infants, is it likely that a future child of this patient will survive? Is any special prenatal care or method of treatment indicated? Should labor again be induced prematurely in spite of the high incidence of this disease in premature infants?

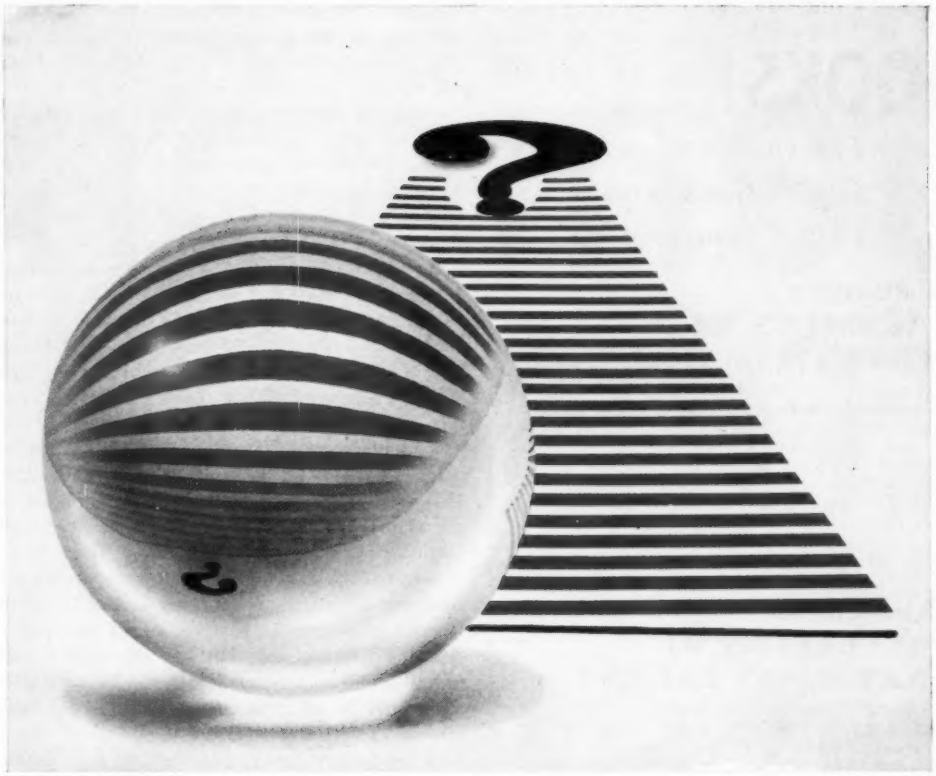
M.D.—New Brunswick

A. Disease of the pulmonary hyaline membrane constitutes the most frequent pathologic finding in premature babies at postmortem examination. In this case, since the three children who died were born prematurely, the prevention of premature labor would appear to be the most important single factor in any future pregnancy. To aid in prevention of premature delivery, nutrition, toxemias and infections should be controlled; prematurely induced labor should be avoided, and appropriate therapy to carry the pregnancy to term should be employed.

A genetic or familial relationship has not been established in hyaline disease of the newborn. Recent reports suggest that increased alveolar surface tension in the newborn contributes to its development. However, the exact cause is unknown and there is no proved effective therapy. Maintenance of fluid and electrolyte balance (some authorities have advocated using a lactated glucose solution), positive-pressure breathing, keeping the infant in a highly humid atmosphere, and use of oxygen and proteolytic enzyme therapy have received enthusiastic support at one time or another.

There would seem to be no reason why any future baby carried to term by this patient should be affected by this condition. Obviously, premature induction of labor is contraindicated.

(Continued on page A-22)



what lurks beyond the broad spectrum?

Broad spectrum antibiotics provide the best means of combating pathogenic organisms which range all the way from large protozoa through gram-negative and gram-positive bacteria to certain viruses at the far end of the spectrum.

But beyond the spectrum lurk pathogenic fungi. It is increasingly apparent that fungal superinfections may occur during or after a course of broad spectrum antibiotics.[1,2] Long term debilitating diseases, diabetes, pregnancy, corticosteroid therapy, high or prolonged antibiotic dosage, and other causes may predispose to fungal superinfections.[1,3,4]

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References: 1. Dowling, H. F.: Postgrad. Med. *23*:594 (June) 1958. 2. Gimble, A. I.; Shea, J. G., and Katz, S.: Antibiotics Annual 1955-1956 New York, Medical Encyclopedia Inc., 1956, p. 676. 3. Long, P. H., in Kneeland, Y., Jr., and Wortis, S. B.: Bull. New York Acad. Med. *33*:552 (Aug.) 1957. 4. Rein, C. R.; Lewis, L. A., and Dick, L. A.: Antibiotic Med. & Clin. Ther. *4*:771 (Dec.) 1957. 5. Stone, M. L., and Mersheimer, W. L.: Antibiotics Annual 1955-1956, New York, Medical Encyclopedia Inc., 1956, p. 862. 6. Campbell, E. A.; Prigot, A., and Dorsey, G. M.: Antibiotic Med. & Clin. Ther. *4*:817 (Dec.) 1957. 7. Chamberlain, C.; Burros, H. M., and Borromeo, V.: Antibiotic Med. & Clin. Ther. *5*:521 (Aug.) 1958. 8. From, P., and Alli, J. H.: Antibiotic Med. & Clin. Ther. *5*:639 (Nov.) 1958.

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Second consultant: The information provided in this case is not sufficiently complete to allow accurate definition of etiologic relationships. In general, the two problems presented are premature labor and neonatal death within 24 hours after birth.

Eastman demonstrated that in only 40 per cent of these cases can a causative factor, such as hypertensive disease, placental accidents, untreated syphilis, multiple pregnancy or congenital anomalies, be ascribed to the onset of premature labor. Recently the incompetent cervical os has been assigned a role in the etiology of premature labor, but this factor should be eliminated in any case of recurrent premature labor. Many authors have cited the relationship of infrequent prenatal visits and inadequate nutrition and vitamin supplementation to premature labor. The effect of emotional stress as a cause must also be considered.

Potter reported that 64 per cent of deaths on the first day of life are due to abnormal pulmonary ventilation and anoxia. Approximately 50 per cent of the infants who die after premature birth reveal hyaline membranes. These membranes usually are not found if death occurs less than one hour or more than five days after birth. Gruenwald suggested that the membrane per se is not the main factor causing respiratory difficulty, but that associated intractable atelectasis, which reflects immature development of the lung, is responsible. Other causes of neonatal death, such as obstetric trauma, malformation, "diabetic states," narcosis, syphilis and other fetal infections, hemolytic disease of the newborn, and intrauterine anoxia, always must be considered.

Before this patient attempts another pregnancy she should be re-evaluated completely, both physically and psychologically. In addition to routine studies, the adequacy of the luteal phase of the cycle and thyroid function should be determined and hysterography should be performed. After the defects, if any, have been corrected, pregnancy could be attempted with careful attention to nutrition and vitamin supplementation, frequent prenatal visits, and psychotherapy for both husband and wife. Certainly coitus and physical exertion should be reduced to a minimum. Gentle vaginal examinations should be performed weekly beginning with the seventh month of pregnancy. If there is any evidence of cervical dilatation or effacement, the patient should remain in bed for the remainder of the pregnancy. Labor should not be induced unless there are extenuating cir-

(Continued on page 24)

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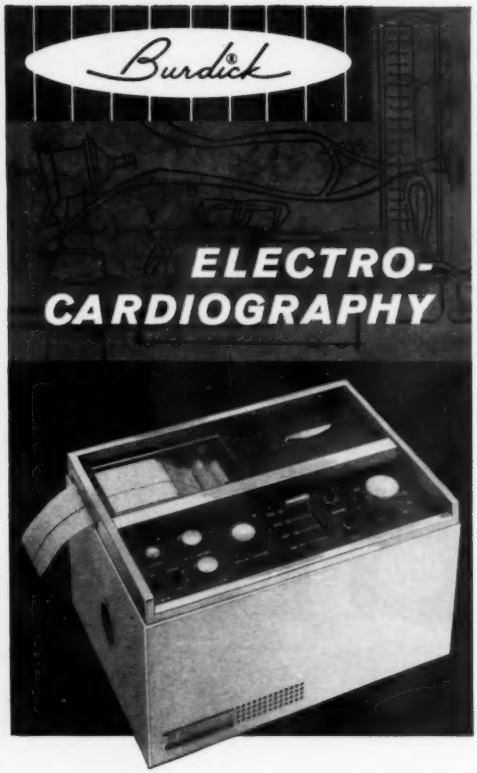

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cumstances. If labor does begin prematurely, a minimum of narcotics should be used. Conduction or local anesthesia would be excellent for delivery, with oxygen being administered for five minutes preceding the anesthesia. The method of delivery should be either spontaneous or with the aid of low forceps and a wide episiotomy.

The immediate care of the newborn should include aspiration of secretions, positional drainage, and incubator care with high moisture content. Oxygen therapy is indicated only if there is evidence of respiratory distress.

The chance of an infant's surviving under these circumstances is sufficiently good to warrant another attempt at pregnancy. However, the patient must realize that the utmost in cooperation will be necessary for a successful outcome.

• BIOZIDENE FORTE FOR TUBERCULOSIS

Q. Is there any truth to the claim made by the manufacturer Schweizberhall, Basel, Switzerland, that the product Biozidene Forte gives better results than do PAS and INH taken separately in therapeutic dosages for treating tuberculosis? Each tablet of Biozidene Forte contains an equimolecular salt of isonicotinic acid, 100 mg. hydrazide, and 500 mg. para-aminosalicylic acid. The dosage recommended is 10 to 15 tablets per day.

M.D.—Philippines

A. I know of no evidence which indicates that the combined isoniazid-PAS tablet gives better results than do equivalent amounts of INH and PAS taken separately. Furthermore, the objections generally attributed to combined therapy apply to Biozidene Forte.

The manufacturer recommends 10 to 15 tablets daily, which would result in a high dosage (1000 mg. plus) of INH and a low dosage (5 gm. plus) of PAS. The usual regimen for the adult patient with tuberculosis includes 300 mg. INH daily, given in one to three doses, and 12 gm. PAS acid or the equivalent amount of a PAS salt daily, divided into three doses given with meals. If the patient is found to be a rapid inactivator of INH, the dosage of INH required will be much greater, and it will be necessary to include 50 to 100 mg. pyridoxine (vitamin B_6) daily to prevent INH neurotoxicity. The dosage schedule for children must be adjusted downward according to weight.

What's happening in Medicine

POSTGRADUATE MEDICINE'S REPORT of late news of interest to practicing physicians

POSITIVE VALUE OF NEGATIVE CYTOLOGY

American Gastro-Enterological Association:

• Exfoliative cytology is intended not only to diagnose carcinoma but also to exclude malignancy. Little emphasis has been placed on this latter aspect. Frequently, clinical conditions, supported by roentgenographic and laboratory findings, are interpreted as positively demonstrating gastrointestinal carcinoma, but the cytologic wash or drainage is negative for malignant cells. When such discrepancies occur, re-evaluation is indicated. The alleged malignancy may be nonexistent, or it may emerge as a medically curable disorder, obviating surgery. —Dr. Howard F. Raskin, University of Chicago School of Medicine, Chicago.

• Evidence suggests but does not prove that hypoproteinemia can result from excessive loss of protein into the intestine. Hypoproteinemia without evident mucosal lesions indicates that an inflammatory exudate is not necessary for intestinal protein loss. The later development of intestinal lesions in these patients suggests that hypoproteinemia sometimes may herald the development of intestinal disease.—Dr. Halsted R. Holman, New York.

FOREIGN MEDICAL TRAINING INADEQUATE

Congress on Medical Education and Licensure:

• A new program for intensive re-education of foreign applicants for internships and residencies in the United States will have to be established. An analysis of the capabilities of foreign graduates shows that the training abroad too often was largely theoretical. Many pass through medical school without ever laying a hand on a patient or listening to a heart murmur. Refresher courses are needed particularly in the fundamentals of biochemistry and physiology and in the related fields of mathematics, chemistry and physics.—Dr. John D. Weir, The Rockefeller Foundation, New York.

IMPRESSIONS OF RURAL PRACTICE

National Conference on Rural Health:

• The physician who goes into general practice in rural areas will find that recognition of his status is often revealed in heart-warming ways that would find difficult expression in the city. Financial security will arrive sooner, because patient capacity will reach a peak much more quickly. The percentage of collections will probably be higher even though fees will differ only slightly. He may also be closer to available cultural and recreational facilities. The amount of learning experience and knowledge gained in the first year is great. —Dr. Jack L. Gibbs, Havana, Ill.

Chemothalamectomy for Intention Tremor

American Academy of Neurology:

• Chemothalamectomy was done in 12 patients incapacitated by intention tremor of such diverse causes as multiple sclerosis, cerebellar degenerative disease, and intracranial trauma. In each instance, intention tremor was relieved without inflicting any neurologic abnormality. Moreover, the extremities previously incapacitated by intention tremor were restored to relatively normal functional capacity. This series has been followed for 18 months.—Dr. Irving S. Cooper, New York.

• A study of 80 cases of intoxication from tranquilizer drugs indicates that these drugs may cause serious extrapyramidal and other central nervous system diseases and should be used with caution. Toxic symptoms are not easily or completely reversed by drugs used for parkinsonism or convulsions.—Dr. Edward E. Shev, San Francisco.

• Palpation of the carotid arteries in the neck and massage of the carotid sinus have been used in physical diagnosis for years. Although it is generally believed that such manipulations produce few if any complications, the authors have seen a number of serious complications. Mechanisms for cerebral infarction associated with carotid manipulation are: hypotension with distal stenosis with or without thrombosis, manual compressive occlusion with or without transient systemic hypotension, reflex vasospasm, embolism from local atheromas, and trauma to the vessel wall with dissecting aneurysm or subsequent thrombosis.—Drs. John R. Calverley and Clark H. Millikan, Mayo Clinic, Rochester, Minn.

Elderly Patients Treatable

National Health Council:

• Any aura of therapeutic nihilism toward the increasing patient population among the aged is unjustified. A variety of psychotherapeutic methods should be tried rather than submit to the fallacy of attributing all emotional disorders to organic cerebral changes.—Dr. Mathew Ross, Beverly Hills.

Optimistic Outlook for Juvenile Diabetics

Missouri State Medical Association:

• An optimistic outlook is warranted in management of children with diabetes mellitus. There is reason to hope that there may soon be practical methods to detect prediabetic patients and means to prevent the development of overt forms of the disease. There is also reason to hope that more specific means of preventing vascular degeneration may be found.—Dr. Robert L. Jackson, University of Missouri School of Medicine, Columbia.

• Unrecognized respiratory acidosis is a frequent cause of death in severe emphysema. It is often precipitated by administering one of the opiate or barbiturate group of drugs or oxygen, or both. There are no postmortem findings to establish the diagnosis.—Dr. Hurley L. Motley, Los Angeles.

• Distinct clinical mitral regurgitation is a clear-cut indication for open heart surgery if surgical repair must be done. The decision to operate in these instances is definitely influenced by the fact that the potential danger of the condition is greater than that of surgery for a stenosed valve, and by the expectation that surgical treatment of mitral regurgitation will improve with the development of an artificial valve for replacement.—Dr. Ormand C. Julian, University of Illinois College of Medicine, Chicago.

• Clinical tests with the newer steroids for treating rheumatoid arthritis in general showed them to have no significant advantages over some of the older preparations.—Dr. Jack Zuckner, St. Louis.

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CLINICAL BRIEFS FOR MODERN PRACTICE

WHY IS DIABETES IN INFANTS SO DIFFICULT TO DIAGNOSE?

Because of the infrequency of the disease in this age group, its sudden onset, the profusion of inconsistent presenting symptoms, and because the accompanying symptoms of anorexia and vomiting are also characteristic symptoms of many other ills of infancy.

Source: Traisman, H. S.; Boehm, J. J., and Newcomb, A. L.: Diabetes *8*:289, 1959.

for those pediatric puzzlers..."A routine urinalysis and blood sugar should be done whenever the possibility of diagnosing diabetes is entertained."*

DIABETES MELLITUS AT AGES 1 TO 5

Order of Frequency of Presenting Symptoms in 110 Patients

Symptoms	No. of Patients	Per cent of total group
Polyuria	93	84.5
Polydipsia	89	81.0
Weight loss	47	42.7
Polyphagia	28	25.4
Anorexia	16	14.5
Lethargy	14	12.7
Enuresis	7	6.4
Vomiting	5	4.5
Irritability	3	2.7
"Craving for sweets"	3	2.7
"Sticky diaper"	3	2.7
"Strong odor to urine"	2	1.8
Glycosuria	2	1.8
Hypoglycemia	2	1.8
Personality change	1	0.9
Boils	1	0.9
Headache	1	0.9
Abdominal cramps	1	0.9

Adapted from Traisman, H. S.; Boehm, J. J., and Newcomb, A. L.*

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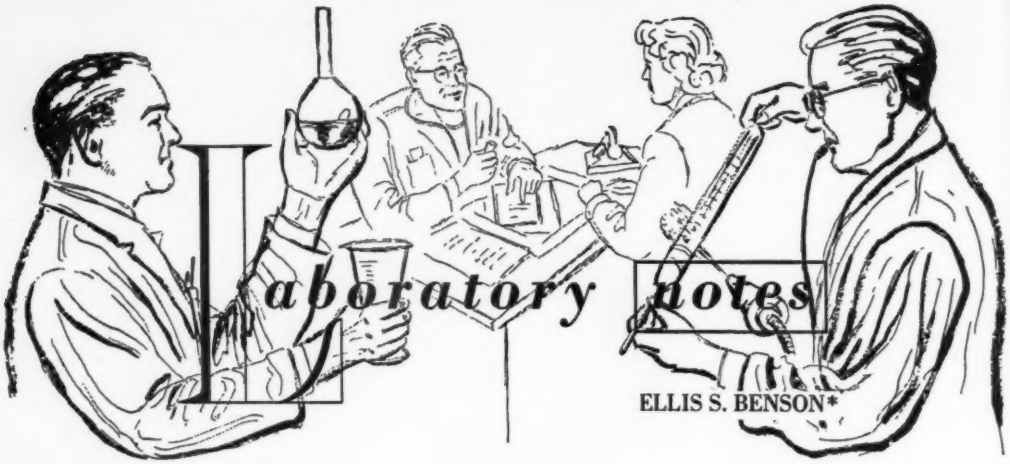


The Laboratory Evaluation of Hemolytic Disease

REX B. CONN, JR.

University of Minnesota Medical School, Minneapolis

Hemolysis, the destruction of red cells, occurs in normal individuals at a rather constant low rate which is balanced by red cell production. When this rate is increased, severe consequences may ensue, the chief of which is anemia. Causes of increased hemolysis are legion, but many of these are rare. The presence of increased hemolysis can be detected readily by laboratory means and most of the causes also can be so traced. Dr. Rex B. Conn, Jr., senior resident in clinical pathology, University of Minnesota, reviews the use of the laboratory in the detection and study of hemolysis.—Ellis S. Benson, M.D.

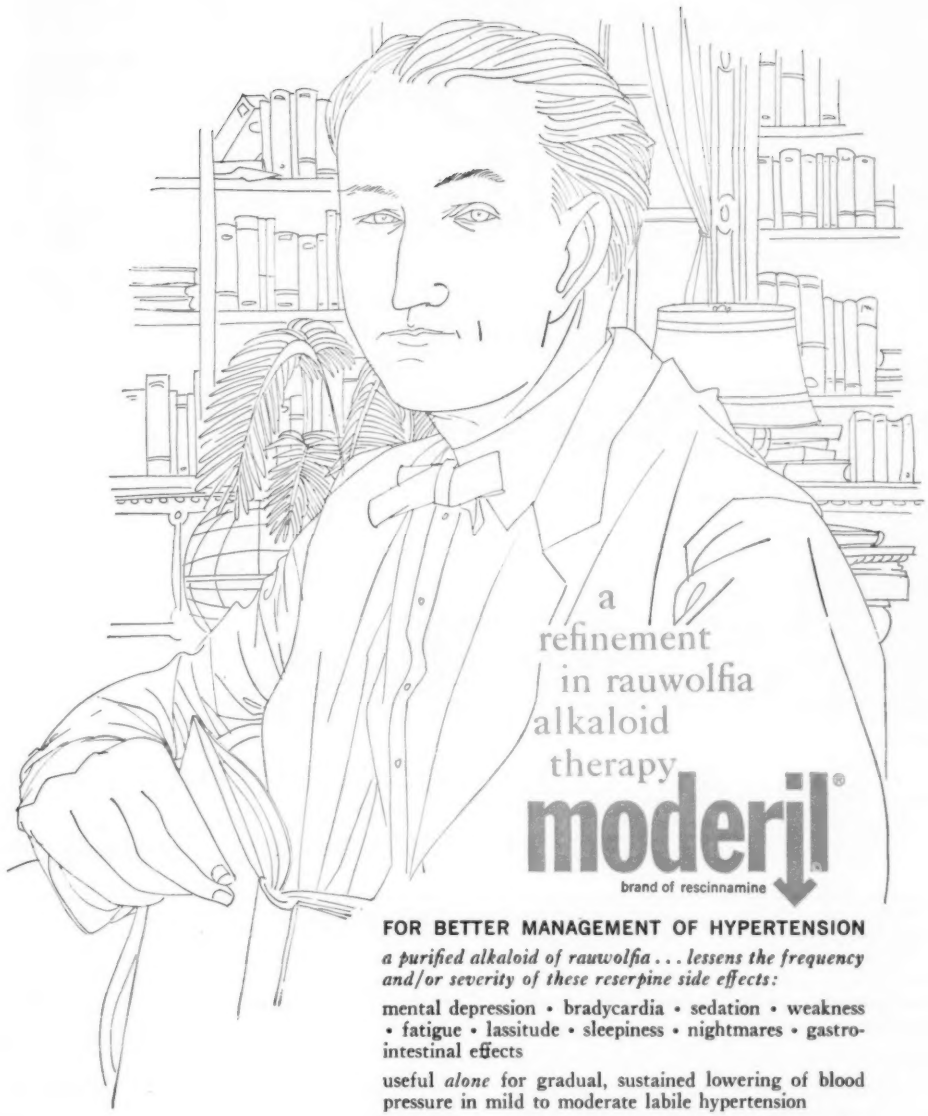
THE physician evaluating a patient with suspected or apparent hemolytic disease relies largely on laboratory data to arrive at a precise picture of the hemolytic process. Selection of the proper tests for each patient and interpretation of the results must be based on an understanding of normal and pathologic formation and destruction of erythrocytes. No single laboratory procedure gives a comprehensive diagnosis, and "shotgun" laboratory requisitions, like the old "shotgun" prescriptions, are wasteful and may miss the diagnosis completely.

REX B. CONN, JR.

Laboratory procedures for the study of hemolytic disease may be divided into three groups: (1) those which measure the rate of erythrocyte destruction, (2) those which detect intravascular hemolysis, and (3) those for investigating the cause of increased hemolysis. Procedures which provide evidence of increased erythrocyte regeneration are also useful in detecting hemolytic disease, but some other conditions which produce similar findings must be ruled out. For example, an increased number of polychromatic erythrocytes usually is found in hemolytic disease, but this also occurs following

(Continued on page A-36)

*Director of Hospital Laboratories and Associate Professor of Clinical Laboratory Medicine and of Pathology, University of Minnesota Medical School, Minneapolis, Minnesota.



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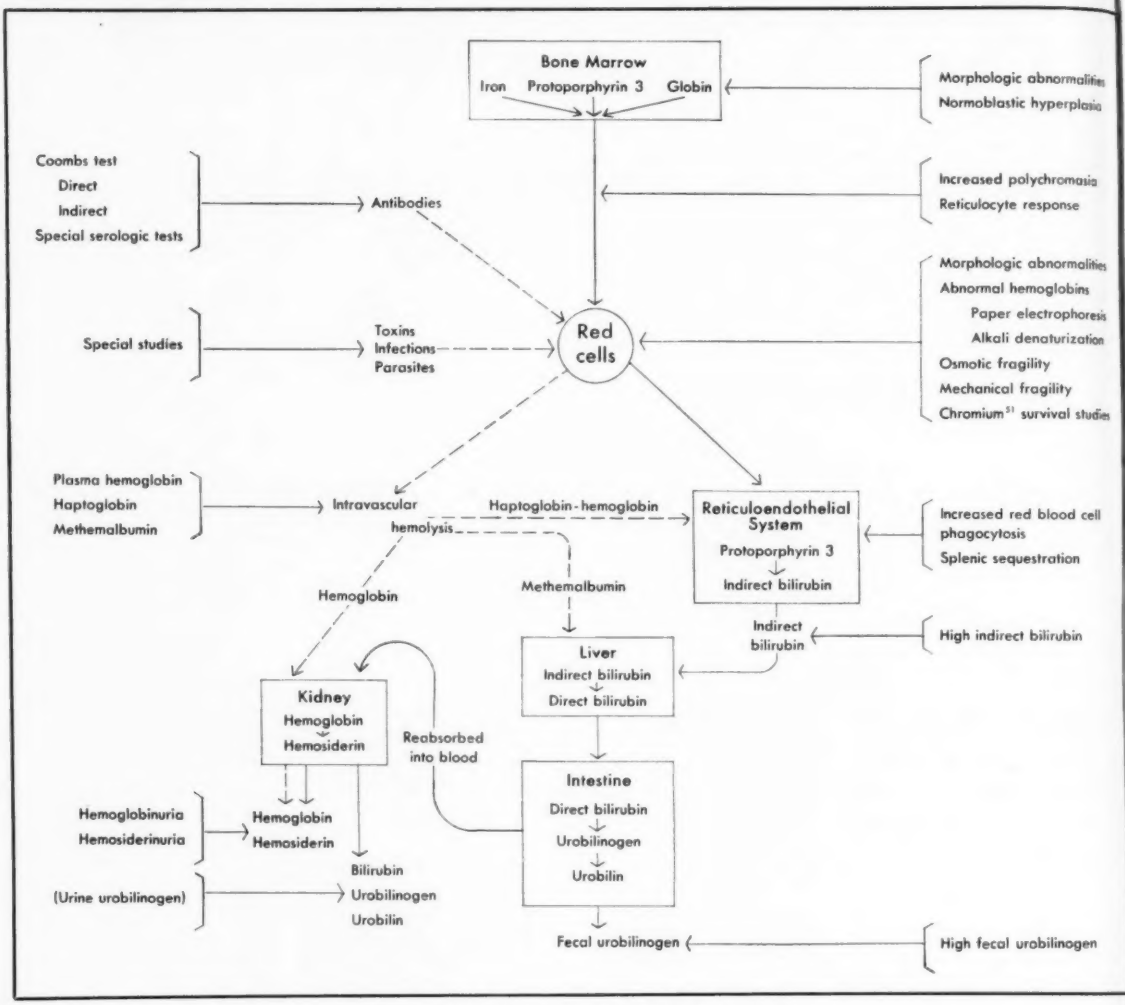

FIGURE 1. Laboratory evaluation of hemolytic disease.

hemorrhage, during B_{12} treatment of megaloblastic anemia, and during the correction of iron-deficiency anemia. In the absence of these other conditions, hemolytic disease should be suspected whenever increased polychromasia is observed.

Increased hemolysis is not accompanied invariably by anemia. In health the average life span of the erythrocyte is 120 days, and, since the total circulating red cell mass for a 70 kg. man is about 2400 ml., there must be 20 ml. of erythrocytes produced each day and 20 ml. destroyed $\left(\frac{2400 \text{ ml.}}{120 \text{ days}} = \frac{20 \text{ ml.}}{\text{day}}\right)$. It has been estimated that the 3000 gm. of marrow in a normal person (3.4 to 5.9 per cent of body weight) can produce six to eight times this many red cells. Anemia, therefore, does not become apparent until the life span of the erythrocytes is shortened to 15 to 20 days. In many cases the marrow is incapable of pro-

(Continued on page A-38)

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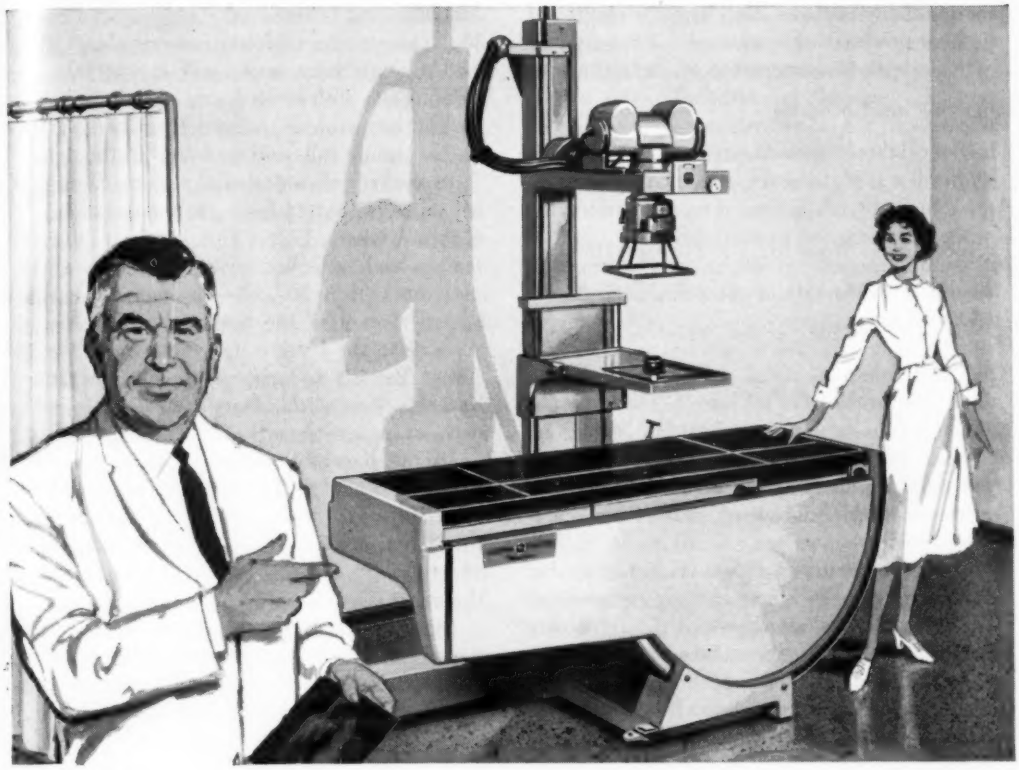

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ducing erythrocytes at such a rate, and the number of red cells drops to the level where the number destroyed each day is equal to the number produced. For example, if the erythrocyte life span is shortened to 40 days, the bone marrow must produce $\frac{2400 \text{ ml.}}{40 \text{ days}}$ or 60 ml. per day of erythrocytes to maintain a normal hemoglobin level. If, however, the marrow can produce only 40 ml. a day, the total circulating red cell mass drops to $\frac{40}{60} \times 2400$ or 1600 ml. At this level the rate of red cell destruction is $\frac{1600 \text{ ml.}}{40 \text{ days}}$ or 40 ml. per day, which is just equal to the number produced. In this case the patient has two-thirds of his normal red cell mass, and the laboratory examination reveals increased erythropoiesis and increased hemolysis. These calculations are from Moore's[1] editorial on the concept of relative bone-marrow failure.

Although the exact mode of destruction of senescent red cells is not entirely understood, it is believed that as they age their fragility to mechanical trauma increases because essential enzyme systems are lost. Most of these aged red cells are destroyed extravascularly in the reticuloendothelial system. The iron of the phagocytized red cells is re-used by newly developing cells, the porphyrin moiety is changed to bilirubin, and the globin becomes part of the body's protein pool.

Destruction of worn-out red cells by phagocytosis is probably the only method of disposal in health. Pathologic destruction of erythrocytes may be caused by either increased phagocytosis or lysis within the vascular space. When the latter occurs, free hemoglobin is released into the plasma and becomes attached by an irreversible process to the alpha$_2$-globulin haptoglobin. Haptoglobin is a mucoprotein (galactose, mannose, N-acetyl glucosamine with protein) which comprises about 20 per cent of the alpha$_2$-globulins and which has the property of combining stoichiometrically with free hemoglobin. The haptoglobin-hemoglobin complex is removed within a few hours by the cells of the reticuloendothelial system.[2] Some of the hemoglobin in the plasma is converted to hematin which becomes attached to the serum albumin, forming methemalbumin, and is removed slowly by the liver.[2] If the plasma hemoglobin exceeds about 90 to 100 mg. per cent, some will escape into the urine. Even with lower levels of plasma hemoglobin, hemosiderin formed from hemoglobin by the tubule cells will be found in the urine.[3]

In the reticuloendothelial system, 35 mg. of bilirubin is formed from each gram of hemoglobin broken down. The bilirubin then is transported, attached to albumin and alpha-globulins, from the cells of the reticuloendothelial system to the liver. The bilirubin on its way to the liver is represented by the indirect fraction as measured in the laboratory, and elevation of this fraction usually is indicative of increased erythrocyte destruction.

In the liver, bilirubin is conjugated with glucuronic acid and excreted as direct bilirubin. Bilirubin is degraded in the intestine through a series of chemical compounds, some of which are reabsorbed and then excreted in the urine.

Figure 1 illustrates the stages from the formation of red cells to disposal of the products of their destruction and the laboratory tests designed to study the various processes.

Determining the Rate of Erythrocyte Destruction

An increased rate of red cell destruction is diagnostic of hemolytic disease whether or not anemia is present. There are two approaches to determining this rate: (1) measurement of the disappearance of circulating red cells and (2) measurement of the products of hemoglobin catabolism.

For measuring the rate of erythrocyte disappearance, radioactive tracer methods have replaced the Ashby technic of differential agglutination. When incubated in a solution of radioactive chromate, erythrocytes take up chromium^{51}, which is excreted when the erythrocyte is destroyed; therefore, the average life span of the circulating erythrocytes can be calculated by measuring the disappearance of radioactivity from the blood. Since the life span of the erythrocyte is 120 days, the radio-

(Continued on page A-41)

activity should disappear at a rate of about 0.3 per cent per day after correction for decay of the chromium[51]. Part of the chromium leaks out of the red cells, however, and the measured rate of disappearance is about 1 to 2 per cent per day. Thus, measured by this method, the half-life of circulating erythrocytes is slightly less than 30 days. The shape of the disappearance curve may give additional information. Normally, there is a linear disappearance, indicating that the older cells are destroyed first, while a logarithmic curve indicates random destruction of red cells as would be found in hemolytic disease caused by an extracorpuscular factor.

It should be kept in mind that the radioactive chromium methods can only measure the disappearance of red cells; therefore, they do not distinguish between hemolytic disease and external loss such as might occur in gastrointestinal bleeding.

To quantify the rate of erythrocyte destruction by measuring the products of hemoglobin catabolism, the fecal urobilinogen determination is the most useful. The Ehrlich aldehyde reaction, used for colorimetric measurement of urobilinogen, gives a color with several chemically related compounds, and the reported result is a total of all of these. Even with adequate specimens there are inherent inaccuracies in the method, since only about 90 per cent of the urobilinogen from red cells is recovered, and 10 to 20 per cent of the measured urobilinogen comes from sources other than hemoglobin. The urobilinogen excretion must be evaluated according to the hemoglobin level, since with anemia the urobilinogen excretion may fall within the normal range (20 to 250 mg. per day) even when the erythrocyte life span is considerably shortened. In a normal individual, from 10 to 20 mg. of urobilinogen is excreted per day for each 100 gm. of circulating hemoglobin. Urobilinogen studies should be concluded before any whole blood is given; otherwise, the results reflect the destruction of banked blood as well as the patient's blood.

The indirect serum bilirubin frequently is elevated in hemolytic disease; however, it is an inaccurate index of red cell destruction because it is so dependent on the ability of the liver to conjugate and excrete bilirubin. In hemolytic disease the serum bilirubin is usually 1 to 3 mg. per cent, but it may be entirely normal even with quite severe hemolysis. The serum bilirubin is useful, however, as confirmatory evidence of hemolytic transfusion reaction. In an acute hemolytic episode, the highest bilirubin values are found from three to seven hours after hemolysis.

The urine urobilinogen excretion sometimes is increased in hemolytic disease, but since high values more often are indicative of liver disease, this test should not be used for either detection or quantification of hemolysis.

Detection of Intravascular Hemolysis

Free hemoglobin is released into the plasma only in pathologic states. This may be either an acute hemolytic episode, such as a transfusion reaction, or a slow, chronic process which is not discovered until jaundice or significant anemia is present. Several procedures are available for confirmation and quantification of intravascular hemolysis.

The plasma hemoglobin is the test most frequently used to detect acute intravascular hemolysis, but in chronic hemolytic states plasma hemoglobin may never become significantly elevated. Plasma hemoglobin values are reliable only if hemolysis during venipuncture can be excluded. One sample of blood should be drawn from each arm and the plasma hemoglobin in each sample determined. Results should be discarded and the examination repeated if the duplicate analyses fail to agree. Normally, the plasma hemoglobin is less than 4 to 5 mg. per cent. Levels above 40 mg. per cent produce a pink tinge to the plasma and may be detected simply by looking at the centrifuged blood.

Since hemoglobin does not appear in the urine until the plasma value exceeds 80 to 100 mg. per cent, hemoglobinuria indicates significant intravascular hemolysis. Although red or dark urine should raise the suspicion of hemolysis, the presence of hemoglobin must be proved. The benzidine test may be used for

(Continued on page A-42)

this purpose, or the hemoglobin may be extracted and measured colorimetrically. Spectroscopic examination is necessary to distinguish hemoglobin from myoglobin. Hematuria with subsequent laking of the red cells should be kept in mind as an alternative explanation for hemoglobin in the urine.

Continuing intravascular hemolysis of a degree insufficient to produce significant elevation of the plasma hemoglobin may be detected by the presence of methemalbumin and the absence of haptoglobin. These determinations also may be used to confirm an episode of acute intravascular hemolysis after the plasma hemoglobin has returned to normal. Although haptoglobin is increased in a variety of diseases, it is decreased only in hemolytic disease or acute hepatitis. Absence of haptoglobin indicates that there has been sufficient intravascular hemolysis to cause its saturation and subsequent removal from the plasma. With normal haptoglobin levels, this state corresponds to a plasma hemoglobin level of 30 to 120 mg. per cent in an acute episode of hemolysis.[2] The presence of methemalbumin is additional evidence that intravascular hemolysis has taken place.[2] The presence of methemalbumin and haptoglobin may be determined by paper electrophoresis, using the same apparatus as that used for routine serum electrophoretic studies with the application of special iron stains.[2] Methemalbumin also may be detected by Schumm's test,[2] and haptoglobin by its peroxidase activity.[4]

Determining the Cause of Increased Hemolysis

In an article in this Journal, Castle[5] described the causes of increased hemolysis as "bad red cells," "bad plasma" or a "big, bad spleen." Attention should be directed to each of these, and selection of appropriate laboratory examinations should be determined largely by the information obtained by history and the physical examination.

Available laboratory procedures for the detection of abnormal erythrocytes include the study of morphologic abnormalities, fragility tests, and the detection of abnormal hemoglobins. Alterations in the enzyme and electrolyte contents of the red cells in hemolytic disease are currently being investigated, and eventually the results of these investigations may provide more precise methods for defining many types of erythrocytic abnormalities.

The first step in the study of any patient with hemolytic disease should be the examination of the peripheral blood smear by the physician. Increased polychromasia with erythrocytic anisocytosis and poikilocytosis and, at times, slight basophilic stippling due either to ribonucleic acid or to iron is characteristic of hemolytic disease. If anemia is present, it is a normochromic, normocytic anemia. Howell-Jolly bodies and occasional normoblasts may be seen, indicating an increased rate of erythropoiesis. Morphologic abnormalities which can be recognized in the peripheral blood include the spherocytes of congenital hemolytic anemia and the other rare familial erythrocytic abnormalities. A reticulocyte count can be done to confirm the impression of increased erythrocyte regeneration.

If the peripheral blood suggests some abnormality of erythropoiesis a bone-marrow aspiration is indicated. Characteristically, the marrow is hyperplastic, with an increased number of normoblasts. In some types of hemolytic disease the macrophages in the marrow contain large numbers of ingested red cells, indicating increased phagocytosis as a cause of erythrocyte destruction. Leukemias and other blood dyscrasias, which may be the cause of hemolysis, are sometimes found during the examination of the blood and marrow.

The osmotic fragility is a measure of the resistance of erythrocytes to hypotonic saline and appears to depend primarily on the shape of the cells. Increased osmotic fragility is characteristic of congenital hemolytic anemia but is found sometimes in other conditions such as acquired hemolytic anemia, erythroblastosis, drug intoxications and severe burns. Mechanical fragility tests, in which the erythrocytes are shaken with glass beads, are not widely done, and in many cases the significance of the results is dubious.

If an abnormal hemoglobin is suspected as a cause of hemolytic disease, paper electro-

(Continued on page A-44)

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REFERENCES: 1. Chow, B. F.: Gerontologia 2:213-221, 1958.
2. Chow, B. F., et al.: Am. J. Clin. Nutrition 6:386, 1958.

phoresis should be done. This procedure is adequate for detecting all the known abnormal hemoglobins, with the exception of fetal (F) hemoglobin, but more elaborate analyses may have to be carried out for complete identification of certain hemoglobin types. F hemoglobin may be detected easily by its resistance to denaturization in strongly alkaline solutions. Sickle-cell disease, caused by the presence of S hemoglobin, also may be identified by the characteristic shape of the erythrocytes when incubated under lowered oxygen tension.

Several types of antibodies may be associated with hemolytic disease.[6] Isoimmune antibodies are those formed following the introduction of cells of a different group into the blood stream; these antibodies may be responsible for any subsequent hemolytic transfusion reactions. Autoantibodies of acquired hemolytic anemia are those formed, through unknown mechanisms, to the patient's own erythrocytes. Autoantibodies are of two general types: (1) the warm antibodies, which are active at 37° C. and (2) the cold antibodies, which are inactive at this temperature but which can be detected at room temperature or lower. Both the warm and cold antibodies of autoimmune hemolytic anemia are adsorbed on the patient's erythrocytes and may be detected by the direct Coombs test. The presence of circulating antibodies can be detected by the indirect Coombs test. This test is usually positive in hemolytic disease due to the cold type of antibody, and it sometimes is positive in that due to warm antibodies, especially during exacerbations of the hemolytic process. More elaborate serologic technics sometimes are necessary to detect and identify autoimmune antibodies. These technics include the use of trypsinized red cells, acidification of the serum, and heat inactivation of the serum, as well as such procedures as the Donath-Landsteiner test in cases of paroxysmal cold hemoglobinuria.

In searching for the etiology of a hemolytic process, infections and toxins must be kept in mind. Infections which produce hemolytic disease are usually caused by streptococci, staphylococci, coliforms or clostridia which have in vitro hemolytic activity. Anemia in acute infections is more often caused by hemolysis, while marrow depression is a more likely cause in chronic infections. Protozoans such as plasmodial and leishmanial organisms can produce hemolytic episodes, but of course they are rare in this country. Careful inquiry about exposure to chemicals, drugs and toxins should be included when taking the patient's history.

There are other less commonly used laboratory procedures which provide additional information about the processes involved in the destruction of erythrocytes. Some of these examinations which employ radioactive tracer technics were reviewed by Owen[7] in this Journal. Erythrocyte sequestration in the spleen may be studied by giving chromium^{51}-tagged cells and taking external counts over the splenic area. Another study that indicates whether hemolysis is produced by abnormal erythrocytes or by extracorpuscular factors is the determination of survival of normal cells in the patient and survival of the patient's cells in a normal individual by using chromium^{51}-tagged erythrocytes.

Probably the most frequent observation which calls the physician's attention to the presence of hemolytic disease is a low hemoglobin or hematocrit. An examination of the peripheral blood smear for polychromasia or a reticulocyte count will indicate whether the anemia is caused by decreased erythropoiesis or increased red cell loss through either hemolysis or hemorrhage. Further laboratory procedures then should be done to confirm the presence of hemolytic disease, to measure the rate of hemolysis, and to determine as far as possible the etiology of the hemolytic process. The rarer causes of hemolysis should be kept in mind. Lupus erythematosus, sarcoidosis, ovarian tumors and liver disease can produce hemolytic disease, and it is not uncommon for leukemia or a lymphoma to manifest itself as a hemolytic process. If the patient's condition permits, treatment should be deferred until the investigations are completed and the diagnosis established.

Although some of the more complex procedures for the study of hemolytic disease are

(Continued on page A-46)

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not widely available, it should be emphasized that the detection of hemolytic disease requires only the simplest of laboratory procedures which are available in every hospital laboratory and which can be done in any physician's office.

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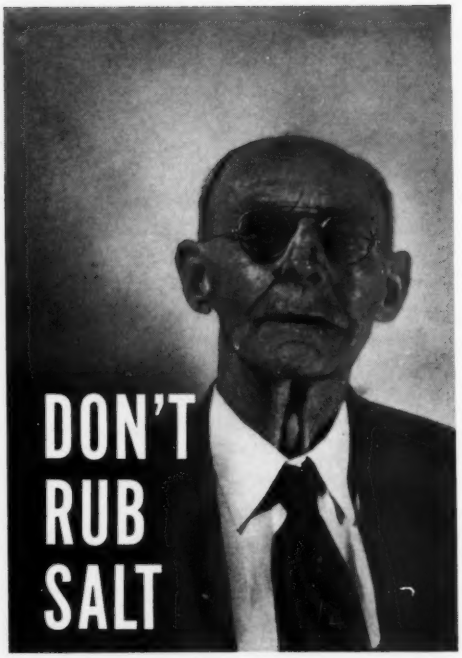

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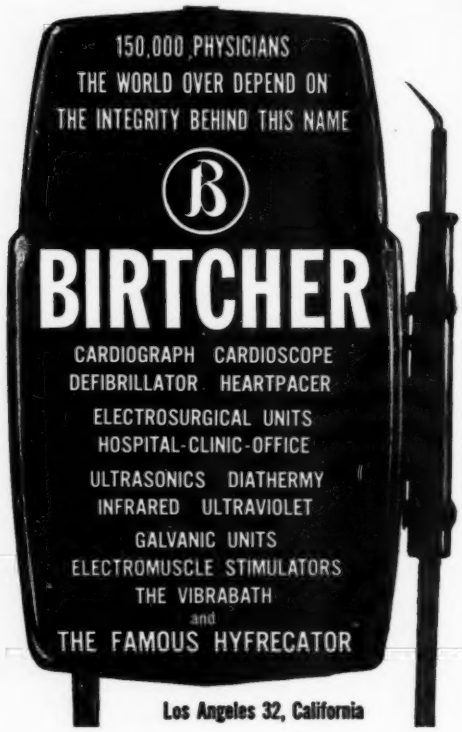

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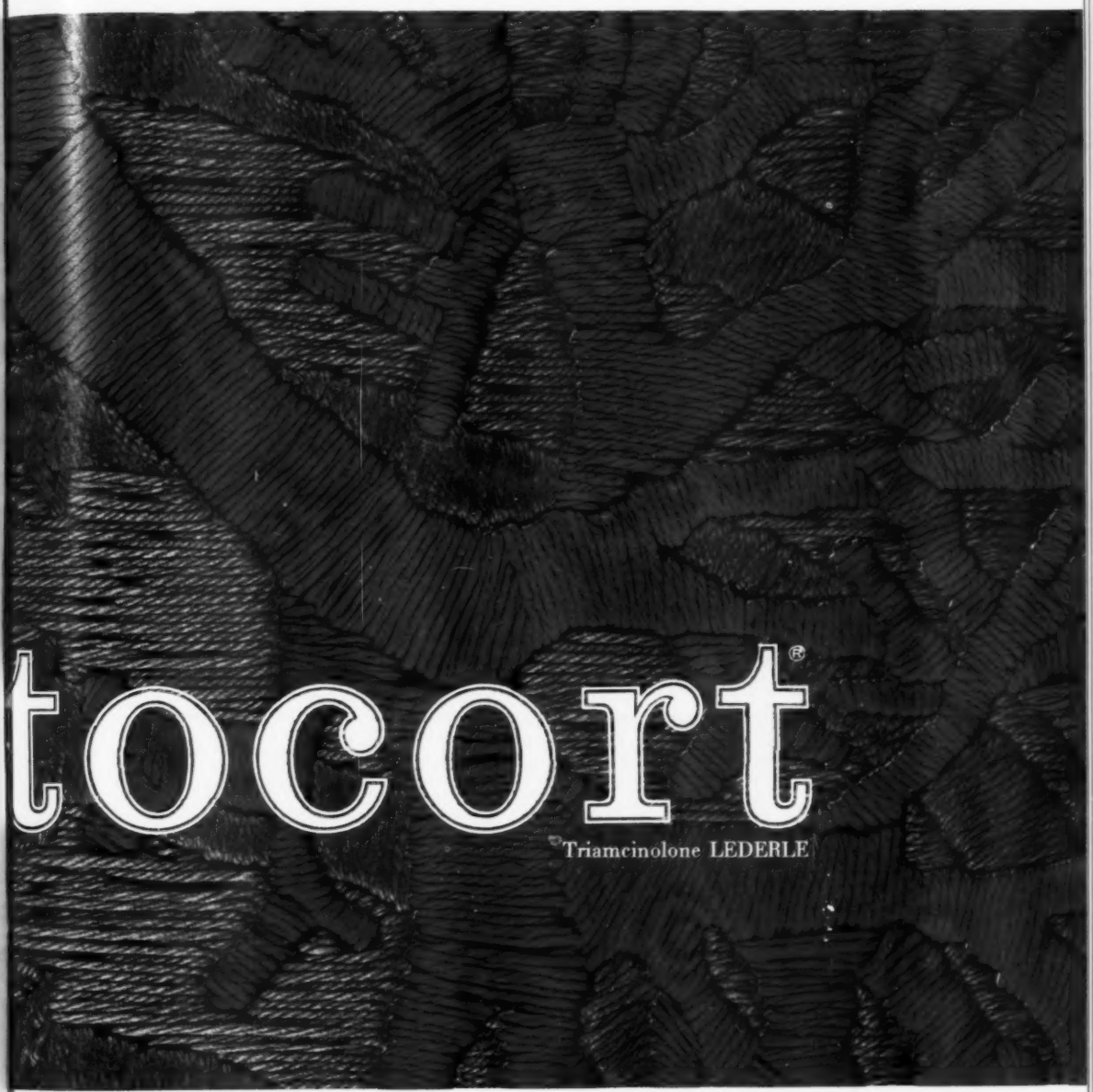

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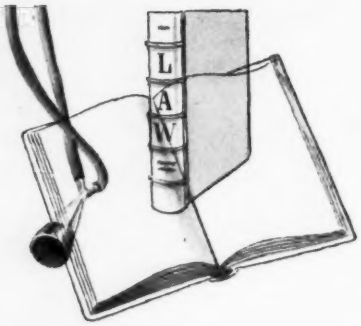

Forensic Medicine

Problems in Establishing a New Medicolegal System

DANIEL J. CONDON*

Phoenix

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"A man without one scar to show on his skin, that is smooth and sleek with ease and home-keeping habits, will undertake to define the office and duties of a general."—Plutarch

DANIEL J. CONDON

EVERYONE in the field of forensic pathology probably is acquainted with the action of the Massachusetts Medical Association in the establishment of the first medical examiner system in 1877. Many features of the Massachusetts system were incorporated in the Medical Examiner's Act of the City of New York, enacted in 1918. Adequate legislation pertaining to medicolegal systems also is in effect in Virginia, Maryland, Rhode Island, Delaware and Arkansas.

In western states, however, legislation regarding medical examiner systems has moved at a slower pace. This probably is due to the tremendous area to be served and to the widely scattered areas of population. It was not until 1951 that an efficient medicolegal system was established in Maricopa County, Arizona. Until that time, coroners in this area had disposed of many cases by briefly noting on the death certificate that death was attributable to "apparently natural causes." However, when Phoenix Newspapers, Inc. and Gene McLain, editor of the *Arizona Republic*, with the support of the county attorney, informed the public of the need for a change from such

(Continued on page A-54)

*Medical Examiner of Maricopa County, Phoenix, Arizona.

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IN HYPEREMOTIVE ADULTS does not impair mental acuity	"... especially well-suited for ambulatory neurotics who must work, drive a car, or operate machinery." Ayd, F. J., Jr.: New York J. Med. **57**:1742 (May 15) 1957.	Garber, R. C., Jr.: J. Florida M. A. **45**:549 (Nov.) 1958. Menger, H. C.: New York J. Med. **58**:1684 (May 15) 1958. Farah, L.: Internat. Rec. Med. **169**:379 (June) 1956.

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haphazard methods of investigation, a medical examiner was appointed. Since that time, the population of Phoenix has increased by approximately 95 per cent, and medicolegal examinations have kept pace.

Objectives of a Medicolegal System

In an efficient medicolegal system, investigation of certain types of death is confined to establishing the medical cause of death and, when possible, to explaining the manner of death. According to Leary,[1,2] and to Ford,[3] a properly functioning medicolegal system provides the following services in relation to deaths from obscure causes: (1) protection of the innocent, (2) recognition of murder, (3) accurate documentation of medical evidence, (4) recognition of public health hazards, and (5) recognition of industrial hazards. Society has taken many such steps in protecting its individual members,[4] and a system incorporating these features provides one means by which persons wrongfully accused of the death of another person can be protected. Conversely, it also aids in establishing guilt and in convicting a person who has caused a death by a criminal act.

The public, which will benefit from the establishment of a properly functioning medicolegal system, must enthusiastically support it. Obviously, the only manner in which society can express its support is by the enactment of suitable legislation. The legislature must understand and be familiar with the problems that persons pursuing employment in such a system will encounter.

Perhaps the most noteworthy example of a model law providing for the establishment of a medicolegal system was prepared by the National Municipal League[5] at the insistence of its executive secretary Richard S. Childs. This law was drafted with the help of other outstanding organizations after Mr. Childs, assisted by Dr. Richard Ford of Boston, conducted a preliminary survey of the requirements of an efficient medicolegal system. Because the requirements of the individual states will differ, a model law can serve only as a guide.[6] A state or community may be able to accept only a few principles of the ideal situation outlined; however, it may subsequently adjust its own laws to conform with the problems peculiar to its area.

Legislating independence into the law governing a medicolegal system is of utmost importance. Such an investigative system must be as free of political influence as is possible under our system of government. Political abuses were responsible for the much-publicized misuse of the coroner systems in past years; indeed, the first medicolegal system in this country was established to eliminate such abuses.[7] Many words and phrases have been used to describe the manner in which coroners sought fees and favors by designating some deaths as suicides or homicides or as accidental when they actually resulted from other causes. In many instances insurance companies were bilked; political cronies were favored, and undertakers waxed rich because of favoritism accorded them.

Disavowal of any attempts toward political control and favoritism is not enough in a medicolegal system. Political expediency raised in the name of economy must be denied. It is no more logical to place a medicolegal system under the control of an existing health department or of a city, county or state hospital than it is to place a public prosecutor's office under the control of the superior and supreme courts of the various states. To function at maximal efficiency, a medicolegal system must be completely independent of all such diverse medical controls, if only because many of the cases which may require investigation in the public interest will be occasioned by accusations of neglect, indifference or maltreatment on the part of the previously mentioned agencies.

It also is true that a competent medicolegal system must not function under the direction of a prosecutor's office. In such a situation, the question of political influence might be a favored method of creating reasonable doubt in the minds of a jury at the time of a trial. For this same reason, it would appear to be equally absurd to relegate such a system to a minor department within an active law enforcement agency. To paraphrase Plutarch,

(Continued on page A-56)

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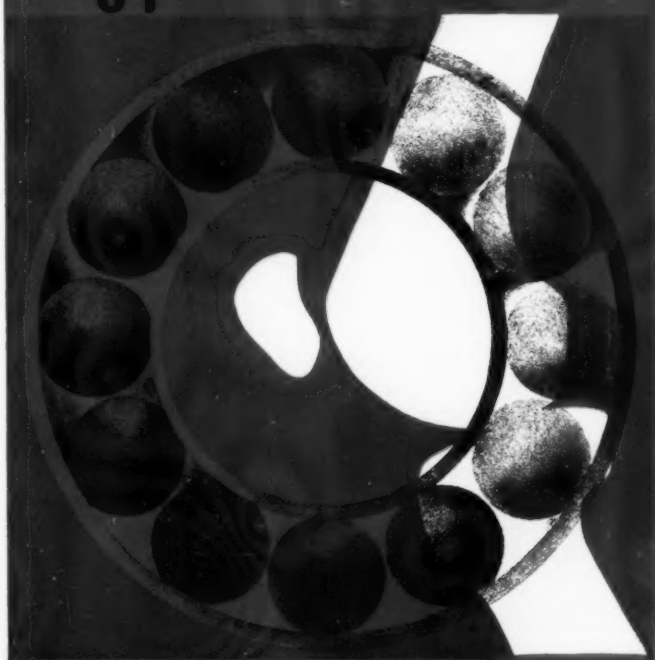

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"Like Caesar's wife, a medicolegal system, to be effective, must be above suspicion."

With the foregoing in mind, all questions relating to the control of a medical examiner system can easily be answered at the time the formation of the system is contemplated. In fact, it is far better for a medicolegal investigator charged with the formation of such a system to operate out of the trunk of his automobile than it is for him to accept domination and control by an already established department in government. A medicolegal system will advance more on its own merits than it will if it is subjected to the disinterested acquiescence of departments which already have been established.

Minimal Requirements of a Medicolegal System

Mortuary—A centrally located and easily accessible building presenting a dignified façade is considered essential for the mortuary in an effective medicolegal system. The various rooms and offices must be neat, clean and easily maintained. In selecting a building or a site for a building, some thought should be given to the proximity of the various courts in which the personnel working at the mortuary will be required to testify.

Examining rooms must be so constructed that they can be easily kept clean, and attendants must be imbued with the desire to maintain meticulously clean surroundings. Adequate facilities for personnel, including showers, dressing rooms, lavatories and sleeping rooms, are as essential as is adequate ventilation in such a building.

The necessity of providing refrigerated vaults of adequate size and capacity for storing corpses needs no elaboration; however, it should be mentioned that provision should be made for making electrodermal temperature determinations before placing the corpses in the vaults. It is most important that standard autopsy tables with adequate lighting (preferably natural) be located in rooms that have extra ventilation. An isolated space for examining decomposed and putrefying bodies also should be provided. A separate room for storage is most helpful; however, if this is not possible, the use of sealed caskets within working spaces is essential.

Preservation of evidence—While it long has been considered standard and accepted medical procedure during the course of an autopsy to remove and retain small shavings or fragments of tissue that might later be used for microscopic examination, there is little, if any, legal precedent favoring this practice.[8,9] Recent legal opinions rendered in the Southwest[10,11] propose that such a practice is illegal unless specific assent is derived from a person who has authority to give such permission. This is primarily a legal problem, and it undoubtedly will be resolved in time.[12,13]

Recent opinions also hold that the practice of removing entire hands from unidentified, putrefying and decomposed bodies for the purpose of restoring fingerprint patterns is a mutilating procedure that the courts will regard with disfavor. We have discontinued such practices in this jurisdiction in Arizona on the theory that our law requires us to determine only the medical cause of death. The question of identification is a statutory determination to be made only by a coroner's jury. I believe that standard medical practice and prudent medicolegal procedure require the continuance of these practices; however, legal protection must be obtained. Obviously, this protection ultimately will ensue.

Other forms of evidence, such as clothing, missiles, etc., should be collected by the medical examiner at the time of his examination and locked in a vault within his control. This preferably is a storage space to which only he has access. If such an arrangement is impractical, such evidence should be adequately marked for purposes of identification and delivered to responsible law enforcement agencies either for purposes of their continuing investigation or for safekeeping.

Photography—The tremendous advantages of photography in relation to the field of forensic traumatology and pathology have been demonstrated repeatedly. No medicolegal system can be considered efficient without some degree of the proper awareness of the value of photographically preserving evidence. Even

(Continued on page A-58)

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in establishing a system "on a shoestring," it is essential that at least one inexpensive camera is included in the equipment.[14] Color photography is superior to black and white, and prints are more desirable evidence than are transparencies. Notwithstanding the additional time and expense, no single item is of more value in an efficient medicolegal system than are good, properly presented photographs.

Statistical data—Although it is not a usual procedure in establishing a medicolegal system, some thought should be given to maintaining data for reports and other statistical purposes. In Maricopa County, our records are maintained by the IBM office. A quick summary of cases, including data varying from the color of the eyes or the length of the body to the percentage of alcohol in the blood or location and nature of a gunshot wound, is almost instantaneously available. While it is desirable, it is not essential that such an elaborate system be used. Initially, our statistical data were recorded with punch cards and codings which we devised as they suited our needs. However, as a means of checking one's work against reports of others in the same field in different localities, some such system must be considered a necessity.

Physicians—To a greater or lesser degree, the eventual success of any medicolegal system hinges on the cooperation of the physicians in the area.[15] Physicians in the state of Arizona, particularly in Maricopa County, long have been on record as favoring adequate legislation covering such a system.

Obviously, there can be no conflict among physicians when a system diligently seeks to establish a cause of death. Physicians recognize the advantage of autopsies and well realize the necessity of having trained observers evaluate any or all information that may assist in establishing a cause of death. As a matter of fact, the only conflict arises when physicians too zealously, in view of the diverse verbiage of pertinent statutes throughout the many states, refer cases to the medicolegal system for the establishment of the cause of death. This practice cannot be criticized, however, because it is a part of the physician's education to the limitations placed on the medicolegal system by the various legislatures.

Insofar as I have been able to determine, there is no jurisdiction in the United States which requires an attending physician to certify to the cause of death beyond a reasonable doubt. In nearly every statute relating to death certificates, the attending physician is requested to use only his best professional judgment.

In some instances, particularly among younger men in this field, there is some dissatisfaction because a medical examiner or a physician-coroner does not and will not use his broad power to conduct an autopsy for the purpose of satisfying scientific curiosity. A review of the many cases settled in various courts of the United States and of the amounts of damages awarded serves as a warning against such practices.

Physicians also occasionally object to the statutory insistence that a medicolegal investigator assume jurisdiction over cases in which persons die from other than natural causes, even though a physician has been in attendance prior to the death. However, even physicians who have such objections later become staunch supporters of a system that insists on thorough investigation to establish not only the cause of death, which information usually is available to the physician in attendance, but also the manner of death, which is more important and which usually is not known by the attending physician. The physician must be made to realize that the manner of death is better determined by a trained investigator. The investigative capabilities of police agencies and the subpoena powers of coroners and inquest juries are more likely to render justice than are the hearsay reports available to an attending physician. When physicians realize the importance of thorough and impartial investigation, they no longer object to this procedure; indeed, they are the first to assist in any capacity in which they are able.

Hospitals—Generally, there is little difficulty in regard to hospitals in the establishment or function of a medicolegal system. The most common conflict occurs when an intern and resident staff seeks permission to perform autopsies. In many instances, relatives have

(Continued on page A-60)

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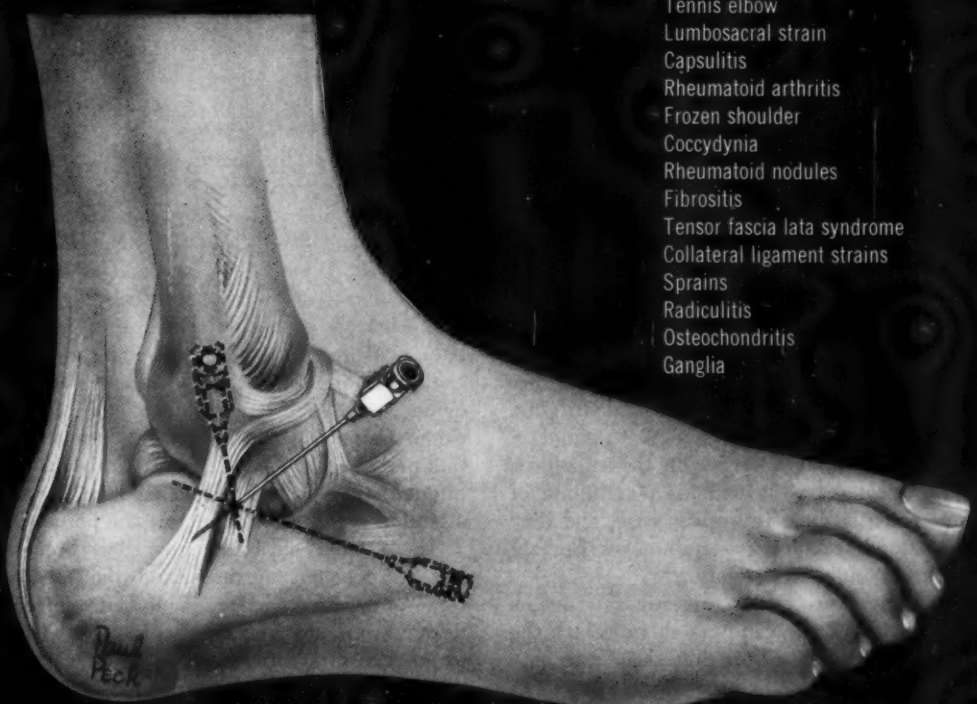

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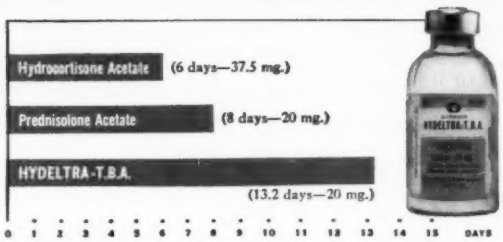
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been threatened or blackmailed into allowing an autopsy, being told that if they did not give permission, the case would be referred to a coroner or medical examiner who would perform an autopsy anyway. It is known that in some public hospitals, bodies have been retained for four or five days while permission has been sought for an autopsy; then, when requests have failed, the cases have been referred for medicolegal investigation.

In view of the many statutes in the United States, most hospital staffs have become increasingly aware of the advantages of medicolegal investigation. This awareness probably was given added impetus by the recent enactment of laws in most states relating to the reporting of gunshot wounds which are treated in hospitals.

The old fear of releasing records of patients who die in hospitals, particularly when those records are important in medicolegal investigation, is fast disappearing. Like physicians, hospital staffs are fully aware of their limitations with respect to investigating facts and circumstances, and they generally are among the first to seek medicolegal advice when it seems to be indicated.

Law enforcement agencies—Of all groups connected with a medicolegal system, the law enforcement agencies are the first to seek and to appreciate its advantages. From his first days in a police academy, a law enforcement officer is taught the advantages of the proper collection of evidence and of identifying, documenting and protecting that evidence. Most police officers have seen justice apparently defeated by the haphazard handling of some essential item in a given case, and they earnestly endeavor to determine each element in a case under investigation.

In many cases, officers investigating deaths falling within their statutory domain lack the essential element of proving the cause and manner of death. When there is no provision to control the disposal of a body or the manner in which the cause of death will be established, society is the loser. In jurisdictions in which adequate medicolegal systems are operating, law enforcement officers are assigned in nearly every instance to investigate facts and circumstances surrounding death. Since a medical examiner or coroner in those systems is charged with establishing the cause and manner of death, it is essential that there be the utmost cooperation between these two offices.

In a newly established medicolegal system, some difficulties may arise concerning the identification and preservation of evidence. In regard to the former, it is essential that the chain of evidence be preserved, as it is in any other type of investigation. If it is practicable, the body should be identified to the examining physician, who then must detail his disposition of the body. In Maricopa County, we have developed an identification card which covers most of the important items relevant to the preservation of the chain. In addition, this card provides a brief summary of the circumstances as observed by the officers who arrived first on the scene of the death.

The medical examiner also may encounter some difficulty in a new system with officers who remove helpful evidence from the body at the scene of the death. Too often, police officers have seen clothing, vital to the presentation of the state's case, disposed of by incineration at the mortuary. Lead missiles, paint chips, hemp fibers, hair and other such trace evidence have been lost when a body has been undressed in preparation for embalming. Therefore, these officers cannot be criticized for their attempts to preserve such evidence. In such circumstances, the medical examiner must assure investigating officers that preservation of evidence is within his line of duty and that the evidence will receive more attention if it is left on or near the body.

There must be full cooperation between law enforcement agencies and the medicolegal examining agency. While law enforcement officers can and do provide the answer to the many puzzling questions that arise in the course of medicolegal investigation, the medicolegal examiner must cooperate to the extent of keeping the investigating officers promptly and fully informed of the results determined by his examination. This information should be supplied in writing.

(Continued on page A-62)

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Other interested groups—Problems encountered in the use of various agencies in medicolegal examinations differ from jurisdiction to jurisdiction. In Maricopa County, a coroner system is used to identify bodies and to determine the manner of death. This system has presented no problems. The referral of cases for examination, the signing of a death certificate listing the medical cause of death, and the further reporting of significant findings to the coroner are statutory requirements and are quite routine.

In some cases, however, conflict might develop when an examining physician is required to provide endless and repetitious testimony at inquests. This is not to say that inquests serve no useful purpose. In many cases generally involving a question relating to the manner of death, the collective judgment of jurors is considered more desirable than is the judgment of a single coroner, medical examiner or law enforcement officer. There also are many instances, particularly in the West, in which tourists and great distances make it desirable to record the testimony of reluctant witnesses under oath during an inquest. In spite of these facts, however, a medical examiner who has presented a written report generally should be exempt from appearing at a routine inquest. In cases which require further elucidation of medical testimony, the medical examiner can and should appear and be as helpful as possible.

Insurance investigations and reports—In Maricopa County, access to reports generally is provided with the permission of the various coroners. They are charged by statute to determine the manner of death, and all inquiries are referred to their offices. Various proof-of-death claims and similar forms submitted by insurance companies relate chiefly to attending physicians, not to coroners or medical examiners. Accordingly, we do not complete such forms, but refer companies or claimants to the Registrar of Vital Statistics for a copy of the completed death certificate.

In almost any accusation of wrongful autopsy or mutilation, there is a bereaved person who has had an insurance claim denied on the basis of the findings in the autopsy. Hence, it follows that in cases in which it is possible it is best to pursue the course outlined in the statutes in regard to releasing information gained as a result of an official autopsy.

Certification—Some progress has been made toward standardizing the form of death certificates. One of the greatest problems in this regard is the requirement on the present certificate that the date and hour of death be stated. In Maricopa County, we do not complete this portion of the certificate, since this may be a matter of judicial determination and since in this locality we frequently have difficulty in establishing the time of death within weeks or months.

Laboratories—Above all, the laboratory used in a medical examiner system must be reliable. Personnel must be well trained and capable, whether the laboratory is an independent agency or is controlled and supervised by the medicolegal examining agency.

Laboratory reports should be in writing and should clearly and precisely relate the findings of the person who made the report. A final opinion in a case requiring laboratory investigation should never be given without the report of the laboratory at hand.

Costs—Any realistic discussion of costs of an adequate medicolegal system must consider the salaries of medicolegal investigators. Persons who devote their professional lives to this sort of work should expect adequate monetary compensation. The salary level should stimulate interest in the work and should provide for a comfortable living, a sense of security, and a relatively early retirement.

Larson[16] indicated his preference for compensation on a basis of fees for services performed. Although many others favor this concept, it does have certain disadvantages. Some medicolegal examiners, if compensated by fees for services rendered, will be reluctant to do an autopsy for fear of being accused of performing it only for the fee involved. A far more intolerable situation is that in which incompetent examiners do the autopsy solely to collect a fee. Another objection to this type of service is the possibility of the selection of a politician's friend to perform the service

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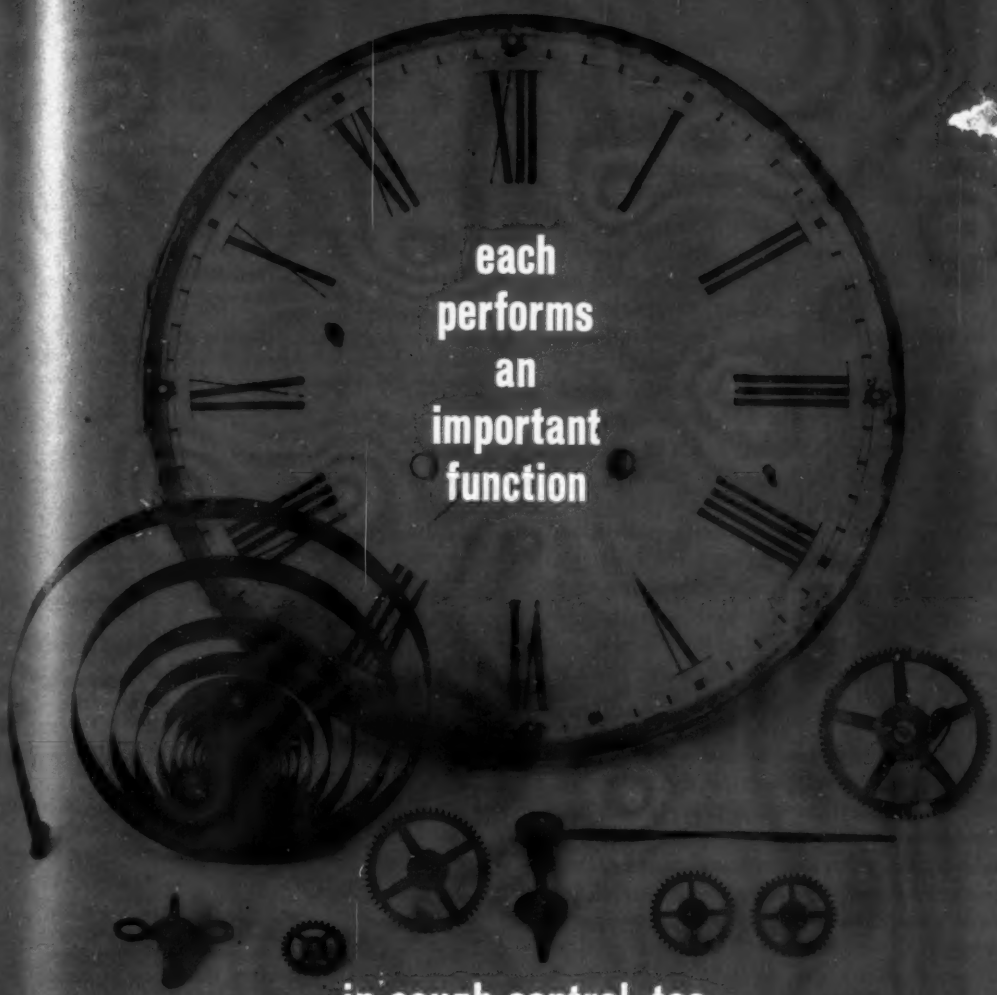

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and [illegible] collect the fee regardless of his ability to conduct a proper medicolegal examination.

In Maricopa County, we combine the paying of salaries with the system of fees for services. In my immediate jurisdiction, all cases requiring investigation by law are investigated and workers are compensated on the basis of an annual salary. Our only criterion for autopsy or external examination is the public interest. On the other hand, if we are required to testify during a civil proceeding at a later date and if we express opinions as expert witnesses, this duty is not considered within the realm of the public interest, and we charge an expert witness fee.

The experience of the presently established medicolegal investigating agencies indicates that the average yearly cost of supporting such a system varies between 4 and 12 cents per capita of population in the jurisdiction involved. In my opinion, such costs are low.

Conclusion

An efficient medicolegal system will be concerned with the development of facts essential to the administration of justice. It will not be concerned with crusades or causes, nor will it be burdened with extravagant theories. Perhaps the most enduring motto of a medicolegal system should be "We serve in the public interest."

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MEETINGS *and Postgraduate Courses*

American Heart Association, St. Louis: Annual meeting and scientific sessions, October 21-25. The scientific sessions will be held October 21-23 in Kiel Auditorium. For further information, write to: Dr. F. J. Lewy, Assistant Medical Director, American Heart Association, 44 East 23rd Street, New York 10.

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Dr. Robert J. Hasterlik, Associate Professor of Medicine at the University of Chicago and Associate Director of the Argonne Cancer Research Hospital, is a graduate of Rush Medical College. After serving with the U. S. Navy during World War II, he entered private practice of internal medicine in Evanston, Illinois. In June 1948 he returned to the University of Chicago as assistant professor of medicine and director of the Health Division at Argonne National Laboratory.

Dr. Hasterlik was a member of the United States delegation to the First International Congress on the Peaceful Uses of Atomic Energy. He has also been a member of two official scientific missions to South America. In the fall of 1957 he served in London as consultant to the United Kingdom Medical Research Council Radium Toxicity Program. He was most recently appointed to the World Health Organization's Expert Advisory Panel on Radiation.—Paul C. Hodges, M.D.

THE fascinating, albeit tragic history of the group of people bearing a significant body burden of radium bears repetition in these particular pages because of the fact that this disease state, except in its major manifestation, has gone unrecognized by the majority of physicians. Present intense interest in the long-range effects of radiation makes imperative an accurate evaluation of any observable effect in any and every human being who is exposed to significant doses of externally administered ionizing radiation or irradiation of the internal environment of the body secondary to the deposition of the long-lived isotopes.

For the past 10 years my colleagues and I at the Argonne National Laboratory and the Argonne Cancer Research Hospital have been studying the effects of the deposition of radium in the skeleton of humans. Why is this important? What do we hope to accomplish? What clinical material is available for study? In addition, what role can the physician engaged in the practice of medicine play in this investigation?

*Emeritus Professor and Chairman, Department of Radiology, University of Chicago, Chicago, Illinois.

FIGURE 1. Multiple areas of bone resorption in the radius and ulna. The smallest areas of resorption present in the midshaft of the radius are typical of the minimal change seen and may be the only finding present.

FIGURE 2. Multiple areas of bone resorption in the skull resembling myeloma, but in this instance caused by radium necrosis of bone. These lesions increase in number and size with time.

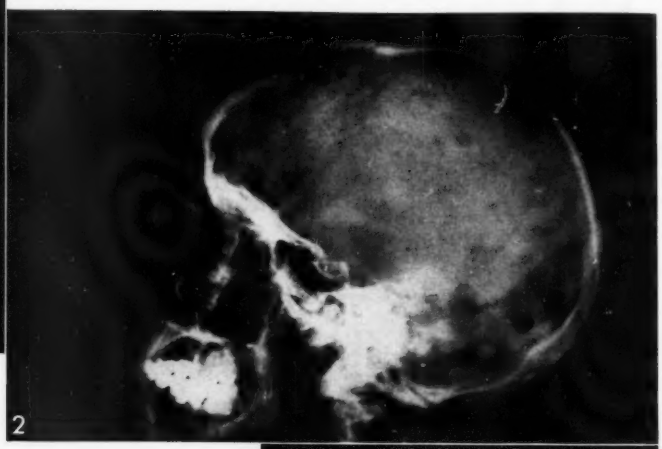

FIGURE 3. Multiple longitudinal areas of bone resorption and coarsening of trabecular pattern which lend a typical streaked appearance to the tibia.

FIGURE 4. Large areas of bone resorption in the midshaft of the humerus.

FIGURE 5. Typical coarsening and smudging of the trabecular pattern in the pelvis secondary to the presence of radium in the skeleton. This patient did not have Paget's disease.

FIGURE 6. Area of bone condensation in the head of the humerus.

FIGURE 7. Atraumatic aseptic necrosis with sequestration of the head of the radius in a radium-bearing patient. Osteosarcoma of the scapula recently developed in this patient, who bears a body burden of 1 μg. radium.

FIGURE 8. Necrosis of the heads of the femurs and the acetabula plus other typical radium changes: bone condensation, trabecular changes and bone resorption.

(Figures 1, 2, 3, 5, 6, 7 and 8 are reproduced with permission of the *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine*.[10])

As emphasized by Dr. Paul C. Hodges[1] in a recent article in this Journal, the collection of statistically valid data concerning the long-range effects of radiation as related to longevity, leukemogenesis and carcinogenesis in the human is of prime importance because the extrapolation of data from studies on the experimental animal is difficult and uncertain. The operating "permissible levels" of the various long-lived bone-seeking radioelements are tied to a prime standard, radium^{226}. At this time it should be pointed out that radium poisoning is the only radioelement poisoning which has been observed or well documented in *man*. Various individuals both within and without the medical profession have made statements such as, "Strontium^{90} *causes* bone tumors and leukemia in man," but the profession should be reminded that strontium^{90}-induced disease has *not* been observed in man, and that what is stated as fact is merely a postulate based on extrapolations from animal experiments.

A certain group of individuals in this country and elsewhere carry in their skeletons a significant burden of radium^{226}, with or without an additional burden of radiothorium or mesothorium, over and above the very minute quantity of radium^{226} present in the bodies of all human beings and derived from food and water supplies. One group of these individuals received the radium during the course of employment as radium dial painters (mainly in the era 1914 to 1926); studies done on these patients in whom sarcomas developed are well known through the classic work of Martland[2-4] and his co-workers Conlon and Knef[5] and Humphries,[6] as well as the work of others.[7-9] Less widely known by the profession is the fact that radium administered orally or intravenously was a popular medication between about 1910 and 1930. The diseases for which radium was prescribed were legion, and the reader is referred to our earlier publication[10] for the history of its use.

It would seem, on the basis of the search of the literature by my colleagues and me, that during the afore-mentioned 20 year period many thousands of individuals were given radium salts intravenously or orally in significant doses. One would expect that many hundreds of persons are still alive who bear a significant body burden of radium and whom we should carefully observe, not only to assess the relationship between the amount of radioactive material present in the body and the degree of bony damage and the induction of bone or other tumors but also to be in a position to treat tumor at the earliest opportunity, should it arise.

For the most part, the bony lesions produced are rarely recognized by the profession as being related to the late effects of radium in the skeleton, and in this presentation I will attempt to elucidate these changes in the hope that many more of these patients may be identified and studied. The reader is referred to two reviews[9,10] of this subject in which the radiographic findings are reported in detail. Since the publication of the previous papers, an intensive program has been underway at the Argonne National Laboratory, the Argonne Cancer Research Hospital, the Massachusetts Institute of Technology, and the New Jersey State Department of Health in an attempt to find and study *all* persons who were former radium dial workers. The Argonne group recently studied an additional 190 former dial painters, and the findings agree qualitatively and quantitatively with those that had been previously reported.[9-11]

Certain roentgenographic changes should elicit a high degree of suspicion on the part of the attending physician or radiologist that the patient was administered radium therapeutically in the past if the history does not bear out that the patient was a former radium dial painter. Parenthetically, it may be added that many of the patients seen by our group were unaware that they had been given radium by their physicians.

Roentgenographic Changes

The roentgenographic changes are well enough known and characterized sufficiently to allow the radiologist to suspect the presence of radium in the skeleton on this basis alone. In addition to these evidences of bone resorption, condensation, aberrant bone remodeling, and infarction, there also occur the well-known

osteosarcomas and the less well-known carcinomas arising in the epithelium of the mastoids and paranasal sinuses.

The *significant* minimal roentgenographic lesions observed by our group have been multiple 1 to 2 mm. by 5 to 20 mm. areas of bone resorption located most frequently in the tibia, fibula, radius, ulna, humerus and femur (figure 1). In addition, with equal frequency, there may be noted punched-out areas of bone resorption in the skull that resemble and must be differentiated from the lesions of myeloma (figure 2). When the small areas of bone resorption are multiple and confluent, they lend a streaked appearance to the bone (figure 3). Infrequently, these lesions may be solitary and as large as 3 to 4 cm. in diameter, and they usually are seen in the tibia, femur or humerus (figure 4).

In addition to the areas of bone resorption, one frequently observes a marked coarsening of the trabecular pattern of the bones, especially in the tibia, fibula, radius, ulna and innominate bones (figure 5). Areas of bone condensation or sclerosis frequently accompany the afore-mentioned lesions. These often are seen in the wings of the ilium and the head of the femur and humerus. They may be as large as 1 to 2 cm. in diameter and resemble the bone infarcts of caisson disease (figure 6). Areas of bone condensation also may be seen at the site of old epiphyseal lines.

Certain major changes also have been observed. Areas of aseptic necrosis, often with sequestration, occur in certain sites of predilection. These are the head of the femur, radius and humerus; the mandible; tarsal scaphoid; and vertebral bodies (figures 7 and 8). Fragmentation of the patella is often observed. In the pathogenesis of this type of bone lesion, the association of radium deposited in the bone and repeated mechanical insult seems apparent. Taken by itself, the presence of one of these areas of aseptic necrosis in an otherwise healthy adult is *not diagnostic* of radium poisoning, but is most suggestive.

Another interesting and suggestive phenomenon is the high incidence of pathologic fractures, especially of the femur, in these patients. The occurrence of fracture after minimal trauma in the absence of tumor and the other causes for pathologic fracture should arouse suspicion of the presence of radium in the skeleton and initiate a search for the other roentgenographically demonstrable bony lesions.

Radium Levels

The reader will quite naturally inquire as to the level of radium in the body necessary to produce these changes. The average human carries about 0.0001 μg. radium in his body, although the burden will differ slightly from this level depending on the radium content of the water and food ingested. Usually, patients were given doses of 10 μg. radium element orally or intravenously each week to a total of as much as 500 to 1000 μg.! The residual body burdens of radium in those patients demonstrating identifiable bony lesions are from 0.4 to 13.9 μg. in our series of patients.

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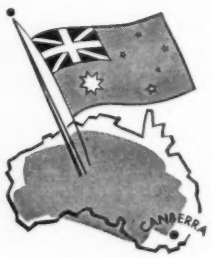
Medicine from Abroad

FROM POSTGRADUATE MEDICINE'S CORRESPONDENTS

AUSTRALIA



Diagnosis and management of pheochromocytoma—Pheochromocytoma is one of the few conditions in which hypertension can be truly cured. In order that treatment may be started before permanent damage to vessels and resulting complications ensue, early diagnosis is of great importance. However, recognition of the disorder is sometimes unduly delayed. In the *Medical Journal of Australia*, Drs. Morris C. Davis and Alfred J. Barnett, Alfred Hospital, Melbourne, discussed three cases of pheochromocytoma. One case was described in detail to illustrate the difficulties of diagnosis, the investigational procedure by which it may be established, and the dramatic benefit obtained from successful operation. The other two cases were discussed more briefly to illustrate different modes of presentation.

It is not practicable to investigate fully all hypertensive patients for possible pheochromocytoma. Thus, it is necessary to determine when the possibility of this condition should be entertained and appropriate tests performed. Although pheochromocytoma may mimic essential hypertension, the following signs should lead one to suspect its presence: excessive variation in the level of blood pressure, pallor, sweating, glycosuria, and the episodic nature of symptoms. Even in the absence of such signs, it is advisable to make certain that this condition does not exist in all cases of malignant hypertension (as indicated by papilledema) and in severe hypertension in young people, particularly those with normal renal function.

In cases in which pheochromocytoma is suspected, in addition to the routine tests for assessing hypertensive disease and excluding other primary causes, special tests are done in order to find evidence of the production of epinephrine and norepinephrine and to demonstrate the site of the tumor producing them.

Treatment consists of removing the tumor. Preoperative oral administration of adrenergic blocking drugs, such as phentolamine or DIBENZYLINE®, may be helpful occasionally, but it did not prove effective in the authors' cases. The operation recently has been made safer by the use of adrenergic blocking agents (such as phentolamine) before and during operation and pressor agents (such as norepinephrine) after removal of the tumor.

Reduction of staphylococcal infection in the newborn—During the past three years, in common with obstetric hospitals elsewhere, the incidence of staphylococcal infection in the newborn has increased at the Royal Women's Hospital in Melbourne. Largely because of this increase, the honorary medical staff of the hospital set up the Infection Control Subcommittee to investigate the problem and to recommend means of control. Drs. Arthur M. Hill, Hildred

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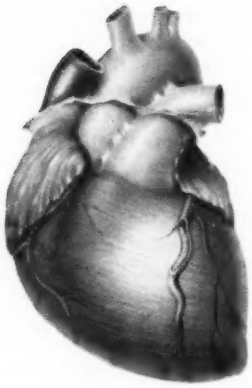
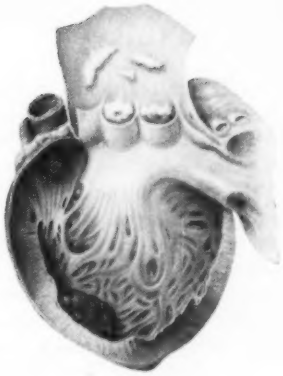


IN ANGINA PECTORIS AND CORONARY INSUFFICIENCY

. . . the treatment must go further than vasodilation alone. It should also control the patient's ever-present anxiety about his condition, since anxiety itself may bring on further attacks.



AFTER MYOCARDIAL INFARCTION

. . . it is frequently not enough to boost blood flow through arterial offshoots and establish new circulation. The disabling fear and anxiety that invariably accompany the condition must be reduced, or the patient may become a chronic invalid.

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M. Butler and J. C. Laver, members of this committee, reported their findings.

The use of hexachlorophene emulsion immediately and effectively reduced the rising incidence of staphylococcal infection in the newborn. In the six months before hexachlorophene was used, the incidence of these infections was 15 per cent; it was only 1.3 per cent in the first six months after treatment with this agent was started. During this trial there was also a decrease in the percentage of babies who became nasal carriers of pathogenic staphylococci. For premature babies the rate dropped from 90 to 30 per cent, and for term babies it dropped from 70 to 38 per cent.

This report was abstracted from the *Medical Journal of Australia.*

AUSTRIA

Idiopathic paresis of the facial nerve—Various theories have been offered to explain the origin of idiopathic facial paresis, but authorities believe that the presence of a swelling in the bony canal of the facial nerve is the immediate cause of impaired function. H. Gstaltner of Vienna experimented with local cortisone treatment, believing that a pharmacodynamic decompression of the facial nerve could be accomplished by injecting cortisone derivatives into the immediate area of the swelling. At the Novotny Clinic, local therapy was given to 10 patients in the form of hydrocortisone (CORTRIL® Suspension) and to 10 others in the form of dehydrocortisone (DELTA-CORTRIL® Suspension). In this experiment, the dehydrocortisone proved superior to hydrocortisone as a therapeutic agent. Patients who had complete peripheral facial paresis of long standing (sometimes of 12 weeks' duration) fully recovered within 5 to 18 days of treatment. A special technic is required to inject the dehydrocortisone anterior to the stylomastoid foramen.

J. Lhotsky of the Neurological Dispensary at Vienna welcomed the new method of treating chronic cases of peripheral facial paresis. At this dispensary, efforts have been made for years to discover a cure for acute peripheral rheumatic facial paresis. In their treatment, Dr. Lhotsky and co-workers have endeavored to avoid the development of the chronic stage of this condition. Their method, shock therapy with CORTIRON® (desoxycorticosterone), has proved to be reliable in most instances; moreover, Dr. Lhotsky was able to discover the reason for the occasional therapeutic failures. This treatment has cured more than a hundred patients and has failed to cure only four. These failures were due to hidden foci or to otologic conditions. Dr. Lhotsky's method is to give the patient a complete neurologic and occasionally an electrodiagnostic examination. After the condition has been definitely diagnosed, the patient receives an intramuscular injection of from 20 to 30 mg. of Cortiron on three successive days. No other treatment is given. In view of the world literature on the subject, Dr. Lhotsky does not recommend the simultaneous use of heat, salicylates or electrotherapy. Dr. Hoff stated that the administration of high doses of vitamin B_1 has no scientific ground. In the opinion of Jacobs and Colony, vitamin B and other hitherto customary measures are contraindicated because they cause edema in the facial canal, which results in the compression of the nerve and paresis. The earlier the nerve is decompressed by means of this pharmacodynamic therapy, the better are its chances for quick recovery. For the same reasons, some authorities recommend early operative intervention.

Desoxycorticosterone, which is a mineral corticoid, differs from the glucocorticoids, cortisone and hydrocortisone. It can never be administered in a harmfully excessive dose, and it is superfluous to employ ACTH in combination with it. Although the usual course of treatment with this agent is one week, complete cure of facial paresis without any residual damage will often occur on the third day.

BRAZIL

Effect of cortisone and ACTH on sedimentation rate—Both in vitro and in vivo experiments have been conducted to determine the effect of cortisone and ACTH on the sedimentation rate in nonrheumatic patients. It was found that intramuscular administration of 200 mg. cortisone or 10 mg. ACTH or oral adminis-

(Continued on page A-88)

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tration of 100 mg. cortisone did not result in a decrease in the sedimentation rate. Two hours after the administration of cortisone, a slightly increased sedimentation rate was observed.

With either blood or washed erythrocytes suspended in a physiologic solution of sodium chloride, cortisone increased the sedimentation rate in vitro; however, the increase in the agglomerative capacity was a result of the solvent solution, not the cortisone.

It was suggested that the decrease in the sedimentation rate observed during hormonal therapy in patients with rheumatic fever is caused not by direct action of the hormones but by improvement of the pathologic process or by a blocking action of some hormones in these patients which increases the sedimentation rate.

Electrocardiographic changes in experimental pneumothorax and hydrothorax—Electrocardiographic changes in pleurisy, such as low voltage of the ventricular complexes and flattening or inversion of the T waves, sometimes with shifting of the R(S)-T segment, are well documented in published literature. The short-circuiting effect of liquids in the pleural cavity causes the drop in voltage, and myocardial alterations or coronary disturbances from mechanical or toxic causes explain the changes in the terminal phase of the ventricular complex. Alterations of the electric axis have also been observed.

In a series of experiments with dogs, an attempt was made to control the electrocardiographic alterations caused by the presence of an electrolyte in the pleural cavity. The toxic-infectious effects were eliminated, and experimental factors, such as the amount of liquid and the respiratory phase, could be varied at will.

The following observations were made from these experiments:

1. Experimental pneumothorax on the left side, with equal intrapleural and barometric pressure, did not cause electrocardiographic changes.

2. The introduction of large amounts of electrolytes into the pleural cavity did not sensibly reduce the potential obtained on the precordium.

3. Neither pneumothorax nor hydropneumothorax caused any alteration in the electric axis in the frontal plane.

4. In both pneumothorax and hydropneumothorax, deflation of the lungs caused a drop in the potential on the precordium; electric axes in the frontal plane did not change.

5. Disappearance of the positive deflection of the ventricular complex, which was observed several times, produced QRS-type complexes in the precordial leads; an occasional tendency to inversion of the T wave was also observed.

6. If the potential obtained on the precordium is conducted through the mediastinal structure, it passes through the posterior mediastinum in dogs and the anterior mediastinum in men.

It was concluded that the condition of the inflated or deflated lung is far more important in the production of low voltage on the precordium than is the presence of an electrolyte in the pleural cavity. In cases of pneumothorax or hydropneumothorax, possibility of obtaining QRS-type complexes on the precordium, with a flattening or an inversion of the T wave, could lead to erroneous diagnosis of anteroseptal infarction of the myocardium.

These reports were abstracted from *Arquivos dos hospitais da Santa Casa de São Paulo.*

ENGLAND

Treatment of fungous infections of the skin—Treatment of superficial fungous infections of the skin for many years has been based on misguided optimism rather than on realism. The fungi which cause ringworm in man are really saprophytes; they live in keratin, surviving and multiplying by digesting their host. If they penetrate too deeply they meet the lethal barrier of living epidermal cells; if they grow downward more slowly than the keratin is being shed, they are cast off. Their survival therefore depends on their ability to grow outward and downward at the same rate as keratin is being formed. Some of them take the suicidal course of exciting an inflammatory reaction, which throws them off or disturbs the production of the keratin on which they live. For this reason the inflammatory types of ringworm, so familiar to the cattleman, have never been a treatment problem. On the other hand, fungi such as *Trichophyton rubrum*, which excite the least reaction in their host, have been impossible to treat. In the same way scalp infections, except for inflammatory kerion, and nail infections have been difficult to cure.

In the *Practitioner*, Dr. David I. Williams,

(Continued on page A-90)

CONSISTENT RESPONSE IN VAGINITIS

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85% SUCCESS:[1,2] TRIBURON VAGINAL CREAM ACHIEVED SYMPTOMATIC CONTROL IN 109 OF 128 WOMEN WITH TRICHOMONAL, MONILIAL AND NON-SPECIFIC VAGINITIS. PARTICULARLY GOOD RESULTS WERE OBTAINED IN TRICHOMONAL AND MIXED INFECTIONS. ONLY TWO INSTANCES OF TRANSIENT BURNING OCCURRED, AND ONLY 11 RECURRENCES WERE NOTED. FURTHER, THE ACTIVE COMPONENT OF TRIBURON VAGINAL CREAM, TRICLOBISONIUM CHLORIDE, HAS BEEN PROVED "NON-IRRITATING...NOT SENSITIZING."[3]

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consulting dermatologist to King's College Hospital, London, has discussed the value of griseofulvin in treating these infections. This substance was isolated from *Penicillium griseofulvum* Dierckx as long ago as 1939, when antibiotics were scarcely heard of, and was first studied for possible uses in the agricultural field. Its activity in vitro was soon demonstrated against dermatophytes, but as a local application it was found to be no better or no worse than many other fungicides. However, in 1958 J. C. Gentles, having found that griseofulvin was relatively nontoxic, thought that it might be effective if given orally in treating fungous infections of the skin, and this has been confirmed by other physicians. The use of griseofulvin has completely changed the treatment of ringworm of the scalp and of favus, although it is wise to insist on other local antifungous measures, including daily application of a fungicide such as Whitfield's ointment and a daily shampoo. Griseofulvin is indicated for infections of the scalp, infections of the skin which do not respond to local treatment, and infections of the nails. No serious toxic effects have been described. It is usually given in a dose of 1 gm. daily until cure is achieved. Apparently it is absorbed from the duodenum, jejunum, ileum, stomach and rectum, in that sequence; no absorption occurs from the colon.

Surgical treatment of atherosclerosis—Irrespective of where the lesion lies, the surgeon can treat a patient who has arterial insufficiency in only one or more of the following ways: arterial reconstruction designed to restore normal or nearly normal blood flow; an operation to increase the efficiency of the collateral circulation; an operation to reduce symptoms by limiting the function of ischemic tissues; and amputation of extremities or excision of ischemic tissues. Arterial aneurysms develop in some patients with atherosclerosis; in such cases the treatment is surgical whenever the location and clinical findings warrant it and the patient's general condition permits it.

At a recent meeting of the Royal Society of Medicine, Professor Charles Rob, St. Mary's Hospital, London, said that while until recently surgeons have concentrated on the management of patients after an artery has thrombosed, he believes that gradually the emphasis will change. The results of surgery in the prethrombotic stage of arterial stenosis are now much better than

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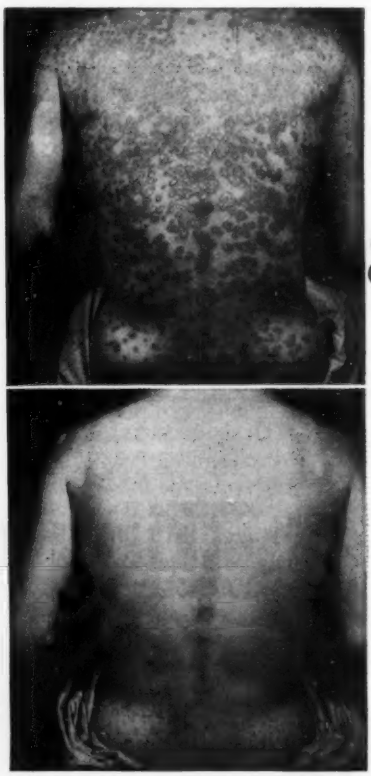

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they were formerly. Professor Rob thinks that in five years surgeons will be concentrating on what in some cases is a curative operation and in other cases is a prophylactic procedure, namely, the removal of arterial stenoses caused by atherosclerosis.

Reconstructive surgery of stenoses of the carotid and vertebral arteries is now an established procedure. Reconstructive surgery of stenoses of the superior mesenteric artery and of the coronary arteries is emerging from the experimental stage and, as skill and knowledge increase, may also become established. Many surgeons already have achieved excellent results in removing arterial stenoses, as opposed to complete thromboses, from the abdominal aorta and arteries of the limbs. The procedures of choice for removing arterial stenoses are thromboendarterectomy and direct suture. With these technics, arterial substitutes such as vein grafts, arterial transplants and plastic prostheses are rarely required. Follow-up studies show much better results when an artery is reconstructed without the use of arterial substitutes.

In diagnosing arterial stenosis, as opposed to thrombosis, Professor Rob has found that arterial auscultation is a particularly valuable physical sign. About half of the patients with severe arterial stenosis whom he has seen exhibited a systolic murmur over the site of the stenosis on auscultation. This serves not only to diagnose the lesion but also to locate it.

Indications for therapeutic abortion—Strict adherence to purely medical criteria means that the indications for therapeutic abortion are shrinking rather than expanding. In practice and because of misplaced sympathy, pressure from colleagues who may see only one side of the problem, and kindred considerations, it is sometimes tempting to modify personal criteria in assessing a particular case. To make an exception, however, nearly always leads to embarrassing consequences. The induction of abortion on flimsy grounds in one case inevitably results in a demand for further operations for equally doubtful indications.

Dr. T. N. A. Jeffcoate, professor of obstetrics, Liverpool University, observed in the *British Medical Journal* that it has not been long since chorea gravidarum, a past history of difficult labor, lymphadenoma, ulcerative colitis, diabetes mellitus, syphilis, adrenal insufficiency, leukemia, purpura, epilepsy, otosclerosis, disseminated scle-

(Continued on page A-94)

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rosis, and many other conditions were acceptable indications for therapeutic abortion. Save in some very special circumstances, none of these criteria is admissible today, in Professor Jeffcoate's opinion.

He pointed out that because of differing views and beliefs among psychiatrists and obstetricians and because an acute anxiety state, possibly accompanied by a threat of suicide, induced by an unwanted pregnancy is regarded as significant by one physician and not by another, psychiatric disorders comprised 40 per cent of the indications for therapeutic abortion in one hospital and were not listed at all in another hospital. During the period from 1938 to 1957 at University College Hospital, London, psychiatric indications for therapeutic abortion were present in 39 per cent of 509 cases. The comparable figure from St. Mary's Hospital, Manchester, was 12.5 per cent; in Dr. Jeffcoate's series of cases in 10 years (1949 to 1958) it was four of 63 cases (6 per cent).

Inherited taints and diseases such as rubella which threaten the health of the fetus are acceptable legally as reasons for therapeutic abortion only when it can be shown that worry over possible fetal abnormality is adversely affecting the mother's health. Rhesus incompatibility can, however, be dangerous to the mother as well as to the fetus. Induction of abortion at present rarely offers hope of improvement or cure of the patient's disease; it generally aims to do no more than to prevent deterioration of the mother's condition, and is therefore more often prophylactic than therapeutic.

FRANCE

Electrotherapy—Electrotherapy has been the subject of numerous reports by French electrologists. Moynier and Guiot reported on the use of electrotherapy in treating paralysis; in *La Presse médicale* L. Stuhl and his co-workers reviewed their experience with this therapeutic procedure.

Stuhl and associates first used this method in treating patients with visual disturbances. Two small wet electrodes were placed on the eyelids, and a rectangular current with enough intensity to provoke phosphenes was used at a rate of one stimulation per second. The rhythm of stimulation was not absolutely regular; the patient had to be able to indicate when the phosphenes appeared. The length of treatments was regulated in order not to inhibit the appearance of phosphenes (either by summation or by confusion) or to provoke somnolence. Each session lasted 10 minutes and was followed by 10 minutes of resting in the dark. The rhythm of stimulation could be accelerated after the disturbances of visual acuity improved, but it had to stay in the range in which phosphenes could be seen.

The degree of visual acuity was increased from 0.4 to 0.7 in 13 of 38 patients with myopia. Fourteen patients were moderately improved, and treatment in seven was considered a failure. Following treatment, the patients generally had better perception of formerly blurred retinal images.

During the course of treatment the authors observed a noticeable improvement in other pathologic syndromes; consequently, they extended the indications for electrotherapy. They modified the placement of electrodes to include a double electrode on the eyelids and another electrode on the spine, or two electrodes on the ears. They continued to use the appearance of phosphenes as a control. When inhibition was provoked the phosphenes disappeared immediately and the current was interrupted. Cerebral excitement was indicated by a prolongation of the appearance of phosphenes for several seconds.

Electrotherapy was effective in patients with (1) sensory phenomena, such as pain, aches after injuries, arthrosis, sympathetic syndromes and anal pruritus; (2) motor phenomena, such as periarthritis and paralysis; and (3) visceral phenomena, including peptic ulcer and asthma. In patients with sensory phenomena, an attempt was made to suppress the zone of cortical projection of the pain. A few of these patients were claimed to be definitely cured, but in others the disappearance of the sensory phenomena lasted only a few weeks or months. However, a second series of electric applications provided faster action and longer relief. In treating patients with visceral phenomena, the objective was to "put in order" the disturbed neural activity.

The authors stated that in this treatment the reticulothalamocortical complex is influenced either by direct passage of the electric stimulations or by diffusion of the current.

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(Continued on page A-96)

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of excitations per second and which occasionally benefit patients with nervous tension caused by agents such as caffeine, can be used in treating neuroses and certain disorders of consciousness and behavior. In general, frequencies lower than 10 impulses per second result in euphoria, especially in patients with a stomach-ache, and frequencies of 20 to 30 impulses per second cause anxiety and recurrence of nightmares.

In order to use electrotherapy correctly, it is necessary to know whether inhibition or stimulation is to be provoked. The diagnosis of disorders of the central nervous system can be very difficult, and the following factors may be helpful in determining the indications for electrotherapy:

1. Classification of the neurologic type of the patient, as given by the Russian school: choleric and sanguine persons who are excited, or phlegmatic and melancholic persons who are inhibited, with variations such as the artist (subcortical predominance) and the intellectual (cortical predominance). The pathologic disorders emphasize the traits of the basic temperament with regard to stimulation or inhibition.
2. Study of conditioned reflexes.
3. Use of electroencephalography which, according to Fessaud and Gastaut, differentiates hyperexcitable and hypoexcitable patients.
4. Use of electromyography, as discussed by Laborit and Guiot.

The authors obtained good results in 65 per cent of their cases by regulating the current according to the appearance of phosphenes and by trying to determine clinically whether stimulation or inhibition should be used. They concluded that electrotherapy is effective for certain disorders of the central nervous system.

GREECE

Gastroduodenal ulcer and vascular disease—At an annual meeting of the Medico-Surgical Society of Athens, Dr. A. Simonetos, head of the III Internal Clinic, State Hospital of Athens, and Dr. G. Kritikos attempted to assess the importance of the vascular factor in the pathogenesis of gastroduodenal ulcer. They reported on 126 cases of gastroduodenal ulcer (29 gastric ulcers and 97 duodenal ulcers) and 496 cases of vascular disease. All patients were treated at the State Hospital of Athens; those with ulcers were observed during the two years prior to this report, and those with vascular disease had been followed since 1947.

The patients with gastroduodenal ulcer were examined for the presence of coexisting vascular disorders of other organs, such as the retina, coronary arteries, aorta, peripheral arteries of the limbs, and kidneys. The second group was studied to determine whether ulcer existed in 80 patients with myocardial infarction, 101 with hypertension, 48 with arteriosclerosis, 32 with nephrosclerosis, 62 with cardiovascular sclerosis, 141 with cerebrovascular lesions, 20 with lesions of the aorta, 11 with arteritis of the lower limbs, and one patient with generalized vascular lesions.

The study revealed that vascular disease was present in only a few of the 126 cases of gastroduodenal ulcer. Myocardial infarction was found in three cases and retinal sclerosis in two; one of the latter two patients had diabetes and was excluded from this series. The incidence of vascular disease in these patients was only 3.17 per cent, and, since the vascular changes occurred many years after the ulcers developed, they probably were related to the patients' advanced age. Ulcer was detected in only eight of the 496 patients (1.61 per cent) with vascular disease (one gastric ulcer and seven duodenal ulcers).

Although clinical, experimental and pathologic evidence indicates that increased gastric acidity and decreased resistance of the gastric mucosa due to vascular changes promote the formation of a gastroduodenal ulcer, the authors found no evidence in this investigation to support the theory that vascular lesions are the chief factors in the pathogenesis of this type of ulcer.

JAPAN

Pulmonary carcinoma—During the fifteenth general assembly of the Japanese Medical Congress, 87 symposia were conducted on general and clinical medical problems. One of the most interesting presentations was that on primary pulmonary carcinoma. Possible causes and development of pulmonary carcinoma were discussed, as well as current research and statistics.

Compared with that of other countries, the death rate from pulmonary cancer in Japan is

(Continued on page A-98)

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rather low. Dr. M. Segi, professor in the department of public health, Tohoku Imperial University Medical Faculty, reported that in Japan the death rate from primary cancer of the lung has quadrupled during the past 10 years. Mortality from this disease has increased by 10 times in the United States and three and a half times in England during the past two decades. In 1956, mortality figures per 100,000 people showed that 55 men in Scotland and 8.1 women in Israel died of pulmonary carcinoma. These were the highest rates in the world. In Japan, death rates from this disease were only 6.8 in men and 2.5 in women. According to the available data, this was the lowest mortality in the world. The age range of persons who died of pulmonary carcinoma was between 65 and 74 years.

Dr. T. Miyaji, professor of pathology, Osaka Imperial University Medical Faculty, reported on 400 autopsies performed in Japan between 1953 and 1958 on patients who had had lung cancer. He pointed out that adenocarcinoma was found more commonly than were other types of lung cancer; this is contrary to reports from the Western countries, in which squamous-cell carcinoma is more frequently observed. Classification of these 400 cases of lung cancer according to cytologic findings revealed that adenocarcinoma was present in 48.9 per cent, an undifferentiated type in 28 per cent, squamous-cell carcinoma in 19.5 per cent, and basosquamous carcinoma in 3.6 per cent. Dr. Miyaji stated that adenocarcinoma is of a more malignant nature than are other carcinomas, and, consequently, tends toward hematogenic metastasis to the lymph nodes in the region of the lungs, liver, pleura, kidneys, adrenal glands and brain.

The causes and development of pulmonary cancer were discussed from the chemical point of view by Dr. M. Ishidate, professor of pharmacology, Tokyo Imperial University Faculty of Medicine; Dr. K. Ota, professor of pathology, Tokyo Medical College, presented the pathologic point of view; and further opinions were given by Dr. E. L. Wynder, Sloan-Kettering Institute, who was a guest at this meeting. Discussions were focused on the possibility that smoking is one of the causes of lung cancer. It was suggested that the epidemiologic and pathologic patterns of primary pulmonary carcinoma observed in Japan differ from those in other countries and that the probability of lung cancer increases with the formation of scar tissue in the lung.

Discussions also included the clinical aspects of lung carcinoma. Dr. H. Honma, head of the department of pulmonary disease, Toranomon Hospital, analyzed the various clinical findings in 207 patients with primary lung cancer seen during the past 13 years. These patients were observed clinically and examined post mortem, mainly at the hospital of the Tokyo Imperial University Faculty of Medicine. Pulmonary tuberculosis was the initial diagnosis in 40 per cent of the patients. Lung cancer was found incidentally at the annual physical examination in 11 per cent; 80 per cent died within 12 months after the initial symptoms appeared.

Dr. S. Okinaka, professor of medicine, Tokyo Imperial University Faculty of Medicine, stated that 11 of the 207 patients showed neurologic symptoms without having any brain metastasis; however, metastatic brain tumors were found post mortem in 41 patients. Fifteen patients had neurologic symptoms initially; in 11 of these, respiratory disturbance due to lung cancer did not develop. These findings demonstrated the need for early diagnosis of lung cancer.

Dr. N. Kawai, professor of surgery, Chiba University of Medicine, and Dr. H. Ichikawa, assistant professor of surgery, Keio Gijuku University Medical College, discussed the prognosis following resection of the lung (including lobectomy and pneumonectomy). Of 167 patients seen by Dr. Ichikawa in the past decade, 68 were operated on and 21 are still alive; however, only two of these patients have survived five years.

SPAIN

Poliomyelitis—In an address to the Royal and National Academy of Medicine, Dr. Juan Bosch Marin, vice-president of the European Poliomyelitis Association, reported on poliomyelitis in Spain. He stated that Salk vaccine is not harmful, in spite of incidents which occurred when it was improperly prepared. Its efficiency in preventing or controlling poliomyelitis has been proved by its use in 300 million children throughout the world. Even if children vaccinated with Salk vaccine have the disease, they seldom die and there are few adverse effects. Vaccination should be done at the beginning of winter so that the person is fully immunized before spring and

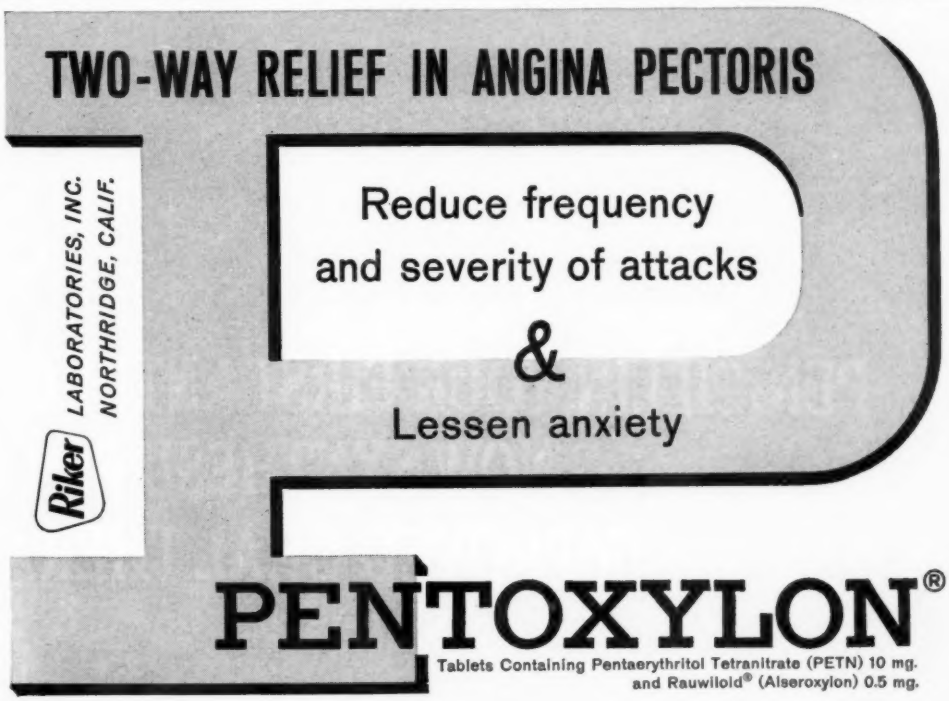
summer, when there is the greatest danger of contagion. It also should be done at a very early age, even before vaccination for diphtheria, tetanus or whooping cough. Dr. Bosch Marin recommended that mothers be vaccinated before giving birth and that babies be vaccinated at four months of age. He also emphasized that patients should not have their tonsils or adenoids removed without having had previous vaccination against poliomyelitis.

In 1959, there were 1,949 cases of poliomyelitis in Spain, a figure greater than that for any previous year. Hospitals in every province are equipped with artificial respirators to be used in caring for these patients. Patients must be prepared psychologically for rehabilitation, and their families and society in general must be taught a different attitude toward invalidism.

Dr. Bosch Marin stated that the National Public Health and Sickness Insurance programs, the benefit institutions, and, especially, the National Rehabilitation Patronage of the Ministry of the Interior are all collaborating in a program of sanitation and social measures for the defense of the country against poliomyelitis.

Tumors of the ureter—Drs. Alfonso de la Peña, Miguel Oliveros and J. Ferrer reported to the Medico-Surgical Academy on four cases of fragmentary resection of the ureter for primary tumor. They stated that the incidence of primary tumors of the ureter is increasing. Formerly, extirpation of the kidney was performed in these cases; however, in the four cases discussed, the tumor was excised without removal of the kidney. The tumor did not recur in any of these patients. In 1956, Dr. Dean stated that any urologic clinic that could find six cases of this type could be considered very privileged. Of 21,173 patients seen during the past 15 years at the University Clinic, 16 have had primary tumor of the ureter.

Only 100 cases of benign tumors of the ureter have been reported in the literature; however, this condition appears to be more common than was formerly believed and it often goes unperceived. The first case in Spain was reported by Tomás de la Maza in 1928. Dr. de la Peña reported four cases of benign tumor of the ureter; the first of these was diagnosed in 1945 and the patient is still in good health. Dr. de la Peña recommends conservative surgery if only one ureter is affected and if the clinical and roentgenographic studies, as well as the function of the kidney, indicate that the tumor is benign.



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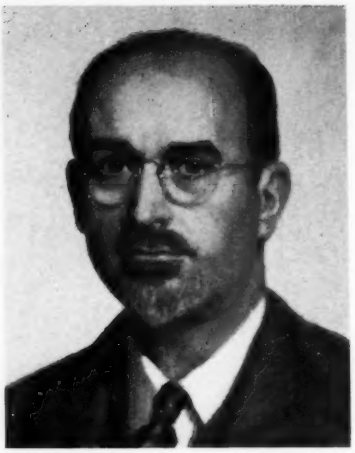

WALTER FREEMAN

FOREWORD

CURRENT periodicals devoted to neurology and psychiatry are filled as never before with technical reports. Many of these investigations represent search and research, and the findings are often conflicting. Furthermore, the details are apt to be beyond the understanding of the reader who is not already deeply engaged in studies in the same narrow field.

This special issue of POSTGRADUATE MEDICINE has been prepared in an effort to clarify some significant advances in the diagnosis and treatment of nervous and mental disorders. The authors are well known in the field of neurology and psychiatry not only for the cogency of their investigations but also for their ability to describe their findings. Here is language that can be understood by physicians not conversant with the technics of neurophysiology, neurochemistry and other basic disciplines.

This is not intended as a treatise; it is not encyclopedic. There is no discussion of epilepsy, poliomyelitis or neurosyphilis. The omission of such subjects does not imply that interest in them is lagging, but rather that other publications, which are readily accessible, deal comprehensively with such disorders. The practical elimination of neurosyphilis, the prevention of poliomyelitis, and the successful treatment of epilepsy have led the editors to focus attention on other fields.

Schizophrenic patients occupy about one-quarter of all the hospital beds in this country. Here is a field worth cultivating. While "the cause" of schizophrenia is still vainly sought, current treatment is restoring many patients to their homes. Parkinsonism and multiple sclerosis are equally obscure in etiology and are often disabling; yet they are not as menacing as they were formerly.

In disease as in geography, there may be discerned four stages: (1) discovery, (2) exploration and mapping, (3) cultivation or mastery, and (4) integration. The papers in this special issue are devoted particularly to integrating the individual problems with the whole field of medicine and thereby enabling the physician to gain confidence in the management of patients.

WALTER FREEMAN, M.D.

Brain Physiology and Modern Medicine

J. D. FRENCH*

University of California at Los Angeles School of Medicine, Los Angeles

Recent neurophysiologic discoveries have contributed much to understanding of human behavior and the role of the nervous system in normal and abnormal organic functions.

Addition of the concept of graded cellular depolarization to the "all-or-none" law of neuronal conduction has far-reaching consequences, as emphasized by the fact that it renders obsolete former concepts of electroencephalographic interpretation.

The central brain stem, in addition to having some measure of visceral control, now is known to be critically implicated in "extrapyramidal" motor modulation, arousal response and consciousness, screening of sensory input to the brain, control of endocrine glands, and emotional behavior. Contributions of these physiologic mechanisms to understanding of epilepsy, psychosomatic disease, mental and emotional disorders, and clinical effects of drugs are reviewed.

J. D. FRENCH

THERE can be no doubt that the roots of many, if not all, of the breakthroughs in modern medicine are firmly planted in advances in fields of basic biologic research. One may point to the insulin story classically or to the development of a vaccine for anterior poliomyelitis to illustrate the immense reliance of such vital discoveries as these on enlightenment growing out of investigations in the biochemical, physiologic, virologic and other sciences.

Perhaps no field of basic research has been more active during the past 20 years than has that which deals with function and structure of the nervous system. As a result, enormous illumination has been cast on modern understanding of human behavior and its disorders. But more than that, these neurophysiologic investigations have emphasized the pervasive role which the nervous system plays in the normal and distorted functions of most organ systems in the body.

This review can deal only with a few as-

*Professor of Anatomy and Clinical Professor of Surgery, University of California at Los Angeles School of Medicine; Coordinator, Brain Research Institute, Los Angeles, California.

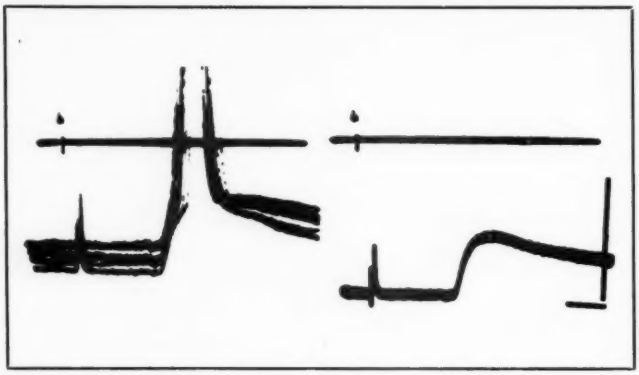

FIGURE 1. These two tracings illustrate the distinction between the "all-or-none" response and the nonpropagated response. Both records are made from within a motor cell in the spinal cord of a cat. The one on the right is made under conditions which prevent the graded response evoked within the cell from reaching threshold, so only the local depolarization wave occurs. On the left, depolarization reaches threshold, and the propagated spike can easily be seen superimposed on the nonpropagated wave.

From TERZUOLO, C. A.: Cerebellar actions upon spinal extensor motoneurons. Arch. ital. biol. 97: 316-339, 1959.

pects of neurophysiology which touch on topics of particular interest to the physician whose interests necessarily are focused on clinical problems. A number of more complete summaries are available and are recommended to those who are stimulated by the illustrative examples submitted here.[1-3]

Functional Brain Mechanisms

The neuron—Two of the most important neurophysiologic discoveries of the recent past have been one which has corrected a fallacious concept of neuronal conduction and another which has elucidated function of the unexplored brain stem. Each of these has expanded, immeasurably, present-day understanding of a great many problems with which the physician must deal commonly.

Older concepts of neuronal function tended to oversimplify both the structure and the excitability of the neuron. A principal inaccuracy proposed that the "all-or-none" law governed all neuronal conductivity. It stated that a nerve cell would display no sign of activity until the strength of a stimulus reaching it exceeded its threshold of excitability, and only then would an impulse be initiated and disseminated throughout the neuron. Now, with refined methods of studying the electric potentials within single cells, it is clearly evident, as Bishop[4] puts it, "that the all-or-none explosive conduction characteristic of nerve fibers is an exceptional, and by no means predominant, form of nervous activity." It is true that the spike, known to originate in the axon itself very near the cell body, displays "all-or-none" characteristics in its conduction throughout the axon. Whether or not this disseminated potential is initiated, however, depends on the excitability of the cell, and this in turn is under the influence of changes in electric potential, arising locally in dendrites and not conducted throughout the cell. Thus, excitatory impulses reaching the dendrite cause the cell to depolarize (increase its negative charge) and raise its excitability to a point where threshold is reached and it "fires." Or, the arriving impulses may be inhibitory in nature, causing the triggering mechanism to hyperpolarize (lower its negative charge), thus lowering its excitability, and to prevent firing (figure 1).

The far-reaching consequences of this new concept of cell function can be emphasized by examining briefly the extensive change it requires in our understanding of the meaning of the electroencephalographic tracing. Formerly, it has been considered that the fluctuations in the record represented composites or envelopes of the conducted spikes of all neurons in the region of the recording electrode. Now, it must be assumed that such is not the case, and that the tracing irregularities largely indicate shifts in dendritic, nonpropagated potentials, hence that they denote excitability rather than discharge. Later, it will be appropriate to indicate how importantly this concept of cell function has added to our understanding of epilepsy.

The brain stem—Probably never in the his-

tory of brain study has there been a mine as rich as the brain stem has been for investigators of the past decade. It was known before, of course, that this core of gray and white matter lying central to the great primary sensory and motor pathways contains the medullary nuclei which mediate reflexes controlling respiratory and cardiovascular stability and, additionally, the hypothalamus which plays a role, then poorly defined, in stabilizing visceral control. Otherwise, little factual information was available to indicate the nature of this core of brain tissue which includes the reticular formation, subthalamus, hypothalamus, midline thalamus and septal region (figure 2). Now, the central brain stem is known to contain, in addition to these visceral control "centers," the principal integrative mechanisms of the brain and is known to express critical influence in a number of modalities of function.

"Extrapyramidal" motor control—The first function to be assigned to this region recognized that it has the remarkable capacity to modify motor movements when stimulated.[5] Excitation of some loci within it causes an increase in on-going movements (figure 3), while stimulation of other regions results in decrease in motor performance. Subsequent investigation defined in detail the extent of this movement-controlling system and revealed it to be that which previously had been known only as "the extrapyramidal system." Present concepts hold that the maintenance of tone and the full range of normal voluntary movement are accomplished by means of motor mechanisms involving these brain-stem centers. These influences are exerted on spinal reflex activity, both by direct downstream conduction from the reticular system and by cephalically directed action on the cortically originating pyramidal tract. For this reason, it is impossible to distinguish functionally between the "pyramidal" and "extrapyramidal" systems.

The arousal mechanism—Soon after the observations were made which elucidated the extrapyramidal system, it was found, almost by chance, that stimulation of this same central core resulted in the arousal of a sleeping

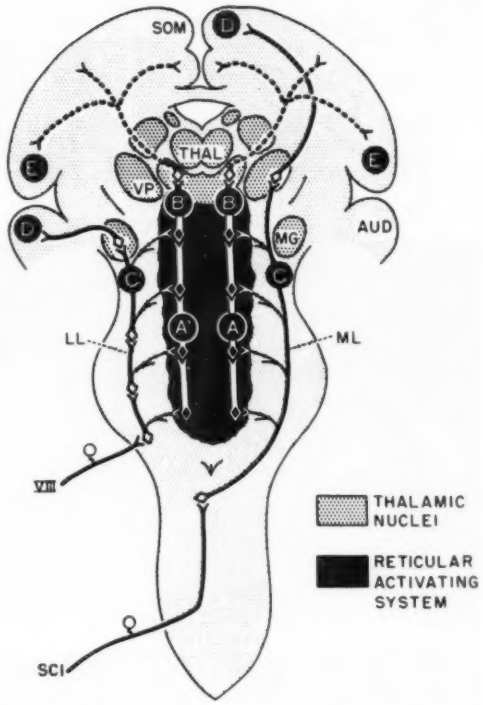

FIGURE 2. This diagram illustrates two peripheral nerves, the sciatic (SCI) and the eighth cranial (VIII), entering the central nervous system and carrying information through long sensory paths C and C′ (LL, lateral lemniscus; ML, medial lemniscus) to primary receiving areas D and D′ of the brain. Additionally, however, they send important branches into the RAS (A-B, black). Stimuli conducted by such branches energize the RAS, causing it to activate the cortex diffusely (dotted lines) and arouse the animal. Additionally, the RAS, activated in this manner, exerts many other influences, described in the text.

From FRENCH, J. D., VERZEANO, M. and MAGOUN, H. W.: An extralemniscal sensory system in the brain. A.M.A. Arch. Neurol. & Psychiat. 69:505-518, 1953.

animal. Since then, countless observations have defined the characteristics of this collection of cells which has come to be called the reticular activating system or RAS. In essence the RAS, by virtue of its ability to exert a tonic excitatory influence on the cortex, contains that mechanism which mediates the state of alertness we call consciousness (figure 2). All stimuli which awaken a sleeping subject or prolong wakefulness in one already aroused do so by "activating" those mechanisms which

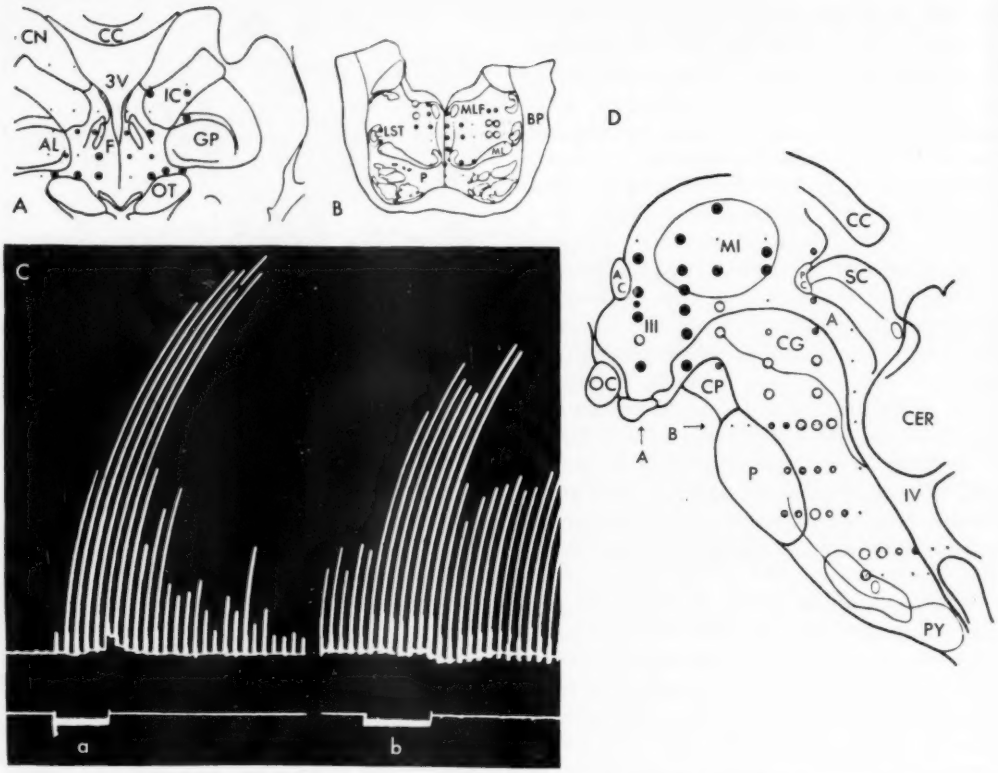

FIGURE 3. A kymographic record (C) of a cat's knee jerk, regularly repeated, shows marked increase in force when brain-stem motor centers, indicated by black dots on the sagittal and cross-section diagrams, were stimulated (a and b). In addition to this "facilitatory" system, there is another system which exerts inhibitory influences on motor activity. Together they represent a major portion of the "extrapyramidal" system.

From RHINES, R. and MAGOUN, H. W.: Brain stem facilitation of cortical motor response. J. Neurophysiol. 9:219-229, 1946.

reside in this central core area. Conversely, anything which injures or interferes with these mechanisms abolishes consciousness. Drugs can do this (mention will be made later of the anesthetic state), or oxygen deficiency or lack of sugar, or any one of literally hundreds of diseases which interfere with the normal metabolism of RAS neurons. All these disorders induce coma.

Control of sensation—In addition to the caudally directed influence of the reticular system on movement and its cephalically oriented powers to control consciousness, another role has been uncovered more recently in the assignment of a sensory-filtering function to the reticular system. It can be shown, for example, that a pulse recorded in the long sensory pathways from appropriate stimulation lower in the tract diminishes in amplitude or even disappears entirely when the central brain stem is coincidentally stimulated (figure 4). Further observations make it clear that the reticular system possesses the remarkable capacity to monitor all information which the brain receives, accepting only a limited amount of sensory input at any one time. Were it not thus, utter chaos would reign, since the cerebral structures could not possibly cope with the overwhelming deluge of impulses with which they are bombarded every moment. No doubt many mental aberrations which characterize psychotic disorders

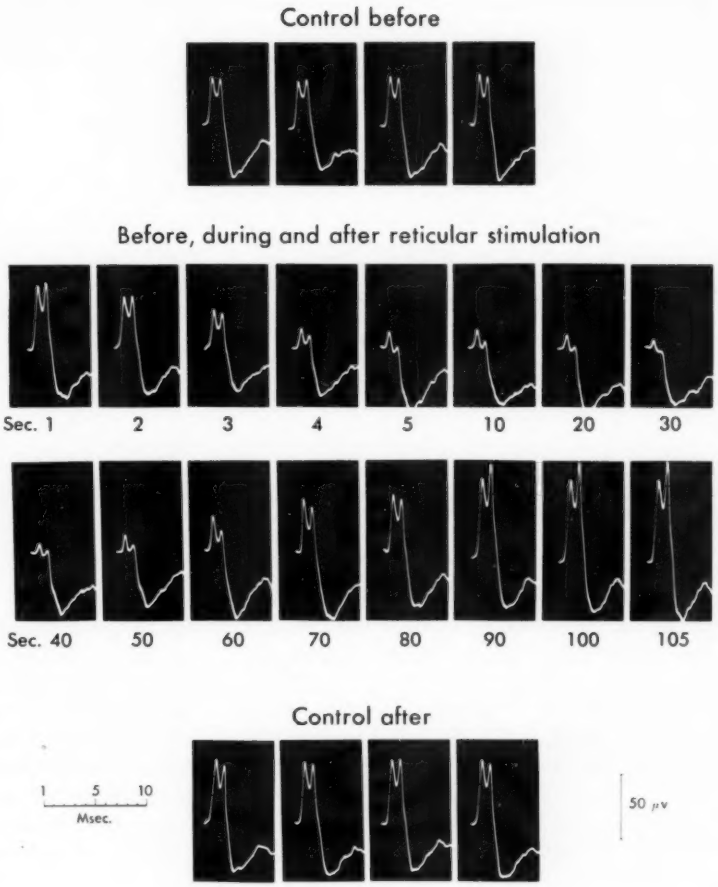

FIGURE 4. These potentials are recorded (on an oscilloscope screen) in the direct sensory pathways for touch (gracilis nucleus) in response to a single shock stimulus applied to a more caudal point in the same tract.

Note that during the concurrent stimulation of the brain-stem reticular formation, by means of another electrode inserted within it (the reticular formation), the lemniscal potential is markedly reduced in size. This mechanism is employed by the brain to protect it from being overstimulated.

From HERNANDEZ-PEON, R., SHERRER, H. and VILASCO, M.: Central influences on afferent conduction in the somatic and visual pathways. Acta neurol. latinoam. 2:8-22, 1956.

are related to distorted function of mechanisms traversing this reticular system.

Control of endocrine glands—Still another discovery during the past decade has assigned to portions of the brain stem a controlling influence over the endocrine system. This control is expressed through action of the hypothalamus on the anterior pituitary body, and it is now evident that pituitary action on all target organs is subject to central influence. Pituitary-adrenocortical mechanisms are particularly heavily implicated in central nervous system function, and the stress reaction, whether of physical or psychologic origin, can be blocked easily in animals by making a lesion in the hypothalamus or by defunctionalizing this brain region through administration of drugs. The importance of this observation will escape no one. Stress is a prevalent commodity in this day and age, and, as will be discussed later, it (stress) is the seed of a multitude of disorders which we have called psychosomatic diseases.

Emotional behavior—Closely linked with neural mechanisms of stress are those known now to be implicated in emotion, for related if not identical portions of the brain stem are involved in each of these behavioral and physiologic states. Here it is necessary to visualize an avenue running (in both directions, of course) from the basal forebrain down through the central hypothalamus into the upper brain stem (figure 5). Traffic from above comes mostly from the primitive forebrain, the hip-

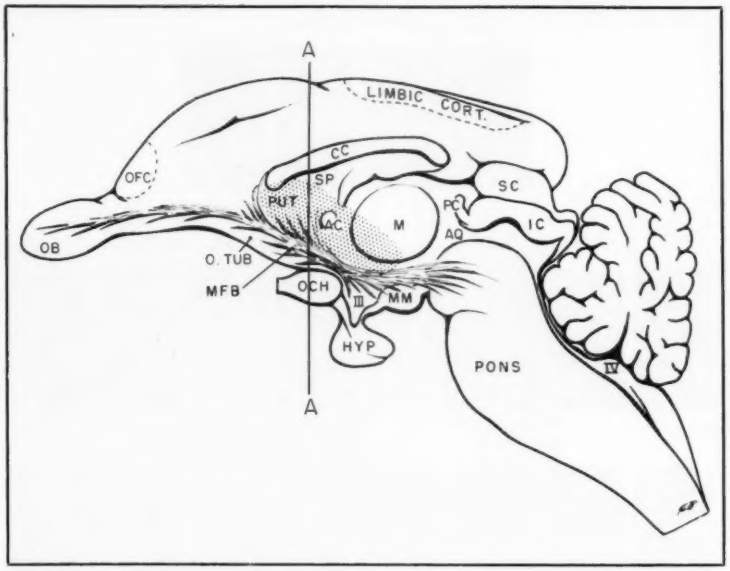

FIGURE 5. This diagram of the rabbit's brain shows the two-way avenue called the medial forebrain bundle (MFB). It interconnects forebrain and brain-stem structures which are implicated physiologically in emotional reactivity and visceral stability. Experiments which stimulate or destroy structures in this area evoke disturbances in emotional behavior and visceral function in animals.

From SAWYER, C. H.: Rhinencephalic involvement in pituitary activation by intraventricular histamine in the rabbit under Nembutal anesthesia. Am. J. Physiol. 180:37-46, 1955.

pocampus, amygdaloid nucleus and limbic cortex, and a host of observations originating with those of Papez[6] in 1937 have linked this neural traffic with "emotionally determined functions pertaining to the preservation of self or to the preservation of the species" (MacLean[7]). Traffic from below comes from the reticular system with its large complement of visceral regulating centers including those particularly susceptible to the impact of pain fibers. This avenue is known as the medial forebrain bundle, and distortion of its normal traffic complement results in emotional instability, prolonged stress and actual visceral disease.

Medical Application

The foregoing illustrations of advances resulting from basic neurophysiologic research are, in their present state of development, important chiefly because they bring enhanced understanding to problems of the clinic. The applications of such basic information to the following common medical problems, however, will serve to indicate the practical importance of the basic experimental methods employed.

Epilepsy—Modern concepts of neuronal electrophysiology have contributed much to knowledge concerning the nature of epilepsy and to revision of many misconceptions concerning this disorder. It is probable that the basic disturbance resides in functionally abnormal dendrites, for the high-voltage, repetitive sharp waves denoting most seizures are characteristic of dendritic depolarizations (figure 6). Presumably the propagated spike discharge is a secondary manifestation of epilepsy, since dendritic depolarizations would certainly be expected to raise excitability of the cells above threshold for firing during wide swings of negativity. There is no doubt, therefore, that cell populations which display trains of waves on the electroencephalogram are functioning abnormally even though they may not actually be "firing" in the old sense as applied to epilepsy.

The search for a therapeutic tool designed to suppress epileptiform activity is greatly aided by the knowledge that dendritic function is at fault, for it is possible to create artificial depolarization phenomena experimentally comparable to those seen in the epileptic state. In animals appropriately prepared, all manner of corrective medications or agents can be tested for their effectiveness in inhibiting such phenomena. The experi-

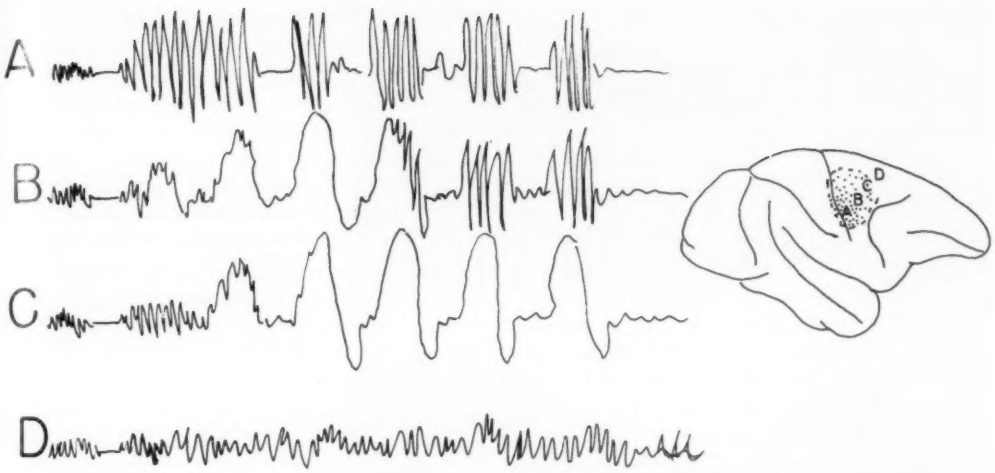

FIGURE 6. The reconstructed electroencephalographic tracings simulate records made from points A, B, C and D during a seizure induced in the brain of a monkey (see diagram). The seizure remains localized to the stippled area on the line diagram, being most intense at A and absent at D. Notice the huge waves in B and C which appear in the tracing before these loci exhibit fast waves characteristic of a seizure discharge. In all probability these waves indicate nonpropagating neuron depolarization and represent a basic defect in epilepsy.

From KONIGSMARK, B. W., ABDULLAH, A. F. and FRENCH, J. D.: Cortical spread of after-discharge in the monkey. Electroencephalog. & Clin. Neurophysiol. 10:687-696, 1958.

mental method, therefore, has become applicable to studies in epilepsy more than at any other time in history, and there is great promise that agents will be found which are capable of reversing the abnormality of cellular function responsible for the disorder.

Psychosomatic disease or disorder—For a long time a relationship has been known to exist between periods of unusual or prolonged stress and the development of certain visceral disorders. Commonly, but not exclusively, this disease-inducing stress has been suspected of being psychologic in origin, due presumably to pressures of our complex modern sociologic environment which are apt to exceed the limits of human tolerance. This suspected relationship between cause and effect has stimulated much speculation, but only recently have neurophysiologic technics been added in any abundance to other methods, including those employing different forms of clinical assessment, in seeking answers to the problem.

An exceedingly prevalent disorder, peptic ulcer, may be taken as a prototype of clinical psychosomatic disturbances in this brief discussion, since it is among the most common disorders of this nature to affect man. It is quite easy to demonstrate in animals that secretion of gastric hydrochloric acid can be increased tremendously by stimulation of specific cortical, hypothalamic and brain-stem loci. Additionally, distortions in gastric tone, motility, blood flow and secretory activity are induced by excitation of these same or closely allied regions. Acute hemorrhages or erosions in the stomach develop in animals in which hypothalamic mechanisms are unbalanced through the placement of small electrically induced lesions. Prolonged stimulation, for weeks and months, in normally behaving monkeys prepared with electrodes implanted in these same hypothalamic regions has resulted in the development of chronic ulcers in the gastric antrum or duodenum which closely simulate clinical lesions (figure 7). It can be supposed that these same brain regions, stimulated artificially or destroyed in experiments, are implicated in the development of peptic ulcers in human beings, and there is every indication that such is the case.

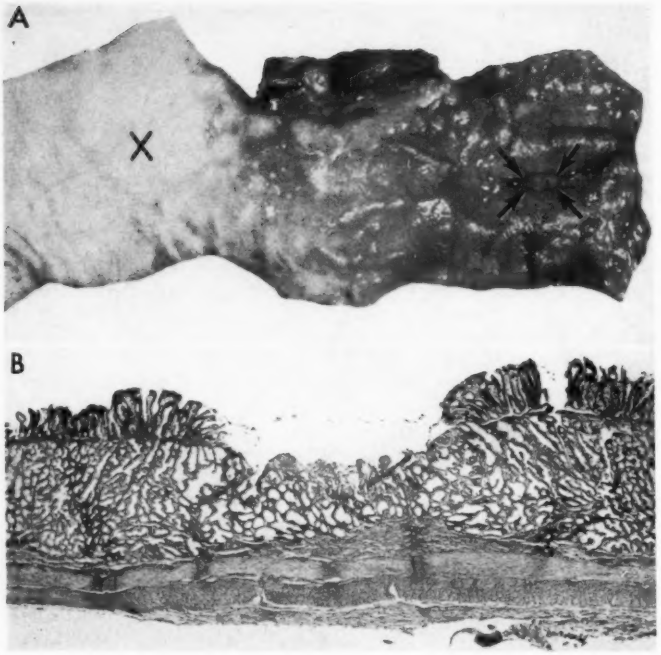

FIGURE 7. The photograph in A shows a punched-out ulcer (arrows) in the duodenum of a monkey stimulated repeatedly in the region of the hypothalamus for over two months.

The photomicrograph in B shows pathologic changes comparable in many ways to those seen in clinical peptic ulcer disease.

From FRENCH, J. D., PORTER, R. W., CAVANAUGH, E. B. and LONGMIRE, R. L.: Experimental gastroduodenal lesions induced by stimulation of the brain. Psychosom. Med. 19:209-220, 1957.

As mentioned earlier, electric stimulation of precisely the loci implicated in the induction of peptic ulcerlike lesions results in the elaboration of other bodily manifestations of stress. A neat series of experiments has served to indicate that monkeys, which do not normally develop ulcers, do so when exposed to stresses comparable perhaps to those responsible for the precipitation of peptic ulcers. These animals (they have been called "executive monkeys") are subjected to highly frustrating behavioral conditioning procedures, both with and without indwelling brain electrodes. A large proportion of these animals have developed peptic ulcers.[8]

In many laboratories, disturbances such as these in the upper gastrointestinal tract are being induced in other organs and systems by experimental manipulation of brain function. Animals stressed chronically, either by brain stimulation or through conditioning, have displayed changes in the ileum and colon which could be compared to ileocolitis. In other studies, cutaneous lesions calling to mind the commonly diagnosed neurodermatitis of the dermatologic clinic have developed in response to such experimental measures. Investigations of great promise employing these technics are in progress which test cardiovascular changes in response to simulated stress,[9] and it is becoming increasingly evident that hypertension, atherosclerosis and coronary insufficiency are conditions which may be justifiably considered as having large psychosomatic components.

Mental and emotional disturbances—Only brief mention may be made here of the contributions of the neurophysiologic laboratory to the overwhelming problem created by the high incidence of mental disturbances in the world. Reference already has been made, for example, to the role which the phylogenetically old forebrain plays in emotionally tinged behavior of animals. Lesions which tamper with these structures, e.g., in the hippocampus of test animals, produce remarkable changes in sexuality, social performance and emotional display. Sham rage or manifestations of terror are evoked by artificial stimulation through electrodes implanted in the midline thalamus

and hypothalamus. Undoubtedly, distortions of function of these systems are implicated in patients with emotional disturbances, including those with psychosomatic visceral disorder, for it is quite apparent that closely related neural mechanisms are involved in the genesis of these conditions.

Local disturbances of function of rhinencephalic and brain-stem neurons characterized by abnormal electroencephalographic tracings —the dendritic depolarization swings or even seizure discharges mentioned earlier—can be elicited easily in experimental animals and usually are followed by abnormal behavior in the test subject. Quite probably, these localized distortions of electric activity, confined to deep structures and not apparent on the standard electroencephalogram, occur in human beings and underlie many mental disorders. Psychomotor epilepsy is a classic example of this kind, for the automatic, inappropriate behavior of patients who have this paroxysmal condition occurs undoubtedly as the result of disordered electric activity recurring focally in the amygdaloid nucleus and hippocampus. The opportunity to explore the depths of the human brain in the course of therapeutic surgery is arising more and more commonly, and localized electroencephalographic abnormality is being found in the septal region, midline thalamic region and brain stem in patients with mental disease. It is quite probable that our mental hospitals are full of such persons who await the development of therapeutic procedures designed to correct this focal brain dysfunction.

Drug effects—Neuropharmacology is a relatively new science but one which serves to emphasize the reflection that all drugs which soothe, quiet, induce sleep, excite, stimulate, immobilize, tranquilize and calm, among other things, do so by virtue of their action on the nervous system. Advancing knowledge of brain function has implemented tremendously understanding of the manner in which this immense class of drugs induces desired effects, for different agents have distinctive affinities for various portions of the brain, hence interfere selectively with diverse brain mechanisms. The sedative and soporific barbiturates, for example, are known to quiet or induce sleep by a selectively depressing action on the RAS. Additionally, they block stress by acting on the posterior hypothalamus, and this property enhances their usefulness in the treatment of psychosomatic and emotional disorders.

Anesthetics have similar depressing effects on the RAS and hypothalamus, but they interfere also with the normal balance of visceral tone mediated by structures in this same central brain-stem core. A recent demonstration of this combined effect on RAS and cardiovascular mechanisms has made possible an explanation of a probable mechanism of cardiac arrest during anesthesia.[9] Responses were recorded in the RAS from single electric stimuli applied to the sciatic nerve. As increasing amounts of anesthetics were then administered, the responses changed in appearance and a late wave appeared on the tracing. Intermittently, throughout the experiment, the cut end of the vagus nerve was stimulated to initiate the cardiovascular reflex response. No dramatic change in heart rate was observed until the late wave evoked in the RAS from sciatic stimulation appeared. At this precise time, vagal stimulation resulted in cardiac arrest. Clearly, brain-stem control over intrinsic visceral reflex activity, stable under lighter or deeper anesthesia, was lost at this exact time during administration of the drug. It follows, of course, that a patient undergoing anesthesia must receive no stimuli, as by intubation, at this stage of induction.

Countless other illustrations of drug, or chemical, action on the brain could be cited. Just as sedatives depress the RAS, stimulants excite it. Agents which cause hallucinations and mimic psychoses distort normal activity of the amygdaloid nucleus and hippocampus. The tranquilizers modify reticular function, particularly that activity which serves to control sensory input to the brain. The technics of neurophysiology—recording of electric activity, stimulating, making lesions and the like in different portions of the brain—have afforded a valuable tool in study of the effects of drug action and can be counted on to disclose many valuable leads in the development of new therapeutic procedures.

Summary

A few recent developments in basic neurophysiology, selected because of their particular impact on topics of clinical interest, are discussed. To the "all-or-none law" of neuronal conduction has been added the concept of graded cellular depolarization, rendering obsolete former concepts of electroencephalographic interpretation. A great amount of information has accumulated concerning function of the central brain stem in addition to that which assigned it some measure of visceral control. Now it is known to be critically implicated in "extrapyramidal" motor modulation, the arousal response and consciousness, screening of sensory input to the brain, control of endocrine glands, and emotional behavior. The contributions which these physiologic mechanisms make to understanding of epilepsy, psychosomatic diseases, mental and emotional disorders, and clinical effects of drugs are reviewed.

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Postgraduate Clinical NOTES

138. STINGRAY STINGS

The standard procedure for treatment of stingray injuries is well established. As the chief complaint is immediate, intense, localized pain, the treatment will be most successful if the victim initiates it. Injuries to an extremity should be irrigated with the salt water at hand, since much of the venom can be washed from the wound by this step. An attempt should be made to remove the integumentary sheath if it can be seen in the wound. If a properly qualified person is available, he may apply a constriction band directly above the wound site. The extremity should then be submerged in hot water at as high a temperature as the patient can tolerate without injury for 30 to 90 minutes. The addition of sodium chloride or magnesium sulfate to the hot water is optional.

F. E. Russell, Stingray injuries, *Public Health Reports*, October 1959, pp. 855-859

Multiple Sclerosis

GEORGE A. SCHUMACHER*

University of Vermont College of Medicine, Burlington, Vermont

In the absence of knowledge of specific etiology or mode of pathogenesis of multiple sclerosis, predictable curative therapy or dependable preventive measures are unavailable. However, numerous empiric or semirational methods to counteract the basic disease process are in use, as well as therapeutic methods for symptomatic relief and for treatment of complications.

Symptomatic therapy remains the most important aspect of the management of patients with multiple sclerosis. As a background for whatever measures of therapy are directed toward the patient, the physician should demonstrate willingness to care for the multiple sclerosis sufferer and to preserve an optimistic attitude.

GEORGE A. SCHUMACHER

MULTIPLE sclerosis, one of the most prevalent of nervous system diseases, often striking in the prime of youth, exacts a large annual toll of disability, mental deterioration and death among persons of both sexes throughout the world. Its cause, still unknown after a century of recognition of the disorder, has been termed the most urgent problem of basic neurology and one of the most obscure problems in the whole field of cellular pathology.[1] Among the many so-called primary demyelinating diseases of the central nervous system, multiple sclerosis remains the most common and best known, the prototype of the group.

The disease appears to have a higher incidence in the northern latitudes, but the reason for this is not understood and no relationship to cold weather itself has been demonstrated.[2] The prevalence is roughly 40 to 60 per 100,000 persons in the north in contrast to 11 to 13 per 100,000 in the south.[3] No race has been found immune to the disease, including Negroes in this country, but a singularly low prevalence has been reported in Japan.[4] An estimated prevalence of 250,000 cases has been reported for the United States. Most analyses suggest a slightly higher incidence in women.[5] In a minority of patients, including children, the disease develops before the age of 20 years, and only rarely does it develop after the age of 50. In the majority, the ill-

*Professor and Chairman, Division of Neurology, University of Vermont College of Medicine, Burlington, Vermont.

ness begins in the third or the fourth decade of life.

Pathology

The pathologic process in multiple sclerosis is limited to the central nervous system with primary involvement of the white matter (myelinated fiber tracts) of the brain and spinal cord. The existence of primary vascular changes has been debated. The lesions consist of islands of myelin breakdown which appear to spread by focal diffusion of a myelinolytic agent as yet undiscovered.[6] Early, the circumscribed, sharply punched-out areas of breakdown reveal merely fragmentation of myelin sheaths, preservation of axons, proliferation of scavenger cells (microglia converted to fat granule or "gitter" cells) and some degree of perivascular inflammatory cell infiltration. If the process is not intense or if local resistance factors counteract the pathogenetic mechanism, apparent recovery of the lesions may occur with concomitant disappearance of symptoms. Thus the course may be episodic and remittent. In the majority of the patients, however, recurrent damage in the same or in different areas leads to permanent loss of myelin, destruction of axons, and replacement by scars of glial fibers due to astrocytic proliferation. The scattering of plaques about the brain and spinal cord seriously disrupts conduction pathways and leads to permanent, eventually severe symptoms.

Causation

Attempts to discover the cause of multiple sclerosis have failed to date. It seems likely, however, that current advances in basic research will achieve a solution to the problem of demyelinating diseases in the not too distant future. X-ray diffraction and electron microscope studies of the ultrastructure of myelin[7,8]; the opening up of the broad field of neurochemistry, especially that related to lipids of the brain and demyelination[9,10]; studies of the metabolism and processes involved in the synthesis, maintenance and degradation of myelin[11,12] and investigation of the role of cellular elements in these processes, including neurons and glia cells, especially oligodendroglia[13]; experimental procedures devised to produce demyelination in vitro and in vivo enabling the study of myelin breakdown as a process[14,15]; and the study of immunologic and immunochemical factors in diseases (spontaneous and experimental) in which demyelination is prominent[16,17] are all leading to a gradual understanding of factors relevant to the pathogenesis of multiple sclerosis.

The classic methods of pathology, while contributing greatly to a comprehension of the disease, appear unable to provide the final elucidation of its cause. Vascular obstruction,[18] infection (viruses,[19] spirochetes[20]) and allergic reactions[21] have been proposed as etiologic factors on the basis of pathologic findings. Among these the concept of localized hyperergic tissue reactions would appear to be based on the soundest pathologic evidence.[21] The alleged demonstration of spirochetes through dark-field examination[22] and culture[23] of the cerebrospinal liquid has not been satisfactorily substantiated to date[24,25] or proved to be related to the cause of multiple sclerosis.[26,27]

The *ad hoc* clinical approaches to the investigations of etiology are unlikely to solve the mystery of the cause of multiple sclerosis but have pointed to the possible role of many factors. Among theories of nutritional difficulties, some, such as vitamin deficiency, low fat intake, lead intoxication or copper deficiency due to geographical soil factors, no longer seem likely. A more recently proposed theory of nutritional cause,[28] namely, that of high fat intake producing a harmful hyperlipemia which in susceptible persons upsets the suspension stability of erythrocytes and platelets in the blood leading to vascular lesions of the central nervous system, has not been substantiated. Clinical studies of the role of vascular obstruction,[29] infection,[30] allergy,[31] metabolic disturbances,[32] psychologic factors[33] and hereditary factors[34,35] have reached no further solution to the problem of etiology of multiple sclerosis, though often shedding light on various aspects of the disease. Epidemiologic investigations are continually seeking clues to etiology based on the unusual incidence and distribution of the disease.[3,36]

Correlation of Lesions With Symptoms and Signs

The abnormalities of nervous function are dependent on temporary or permanent loss of conductivity along nerve fiber pathways that make up the long ascending and descending tracts of the spinal cord, the shorter intersegmental fiber bundles of the brain stem, and the large masses of subcortical fiber tracts of the cerebrum and cerebellum. The neurologic dysfunction thus consists of motor and sensory deficits in the limbs and trunk, disturbance of head functions, including visual, ocular, speech and swallowing, and disturbance in personality and mentation. Since asymmetric development of lesions predominates during the earlier remittent stages of the disease, the motor and sensory impairment is apt to be initially asymmetric, but in the later stages the wide scattering of demyelinated and scarred areas leads to a gradual equalization of disturbed functions on both sides of the body.

Involvement of the pyramidal tracts (corticobulbar or corticospinal) at any point from the subcortical white matter through the brain stem to the spinal cord gives rise to weakness with features of spasticity, hyperreflexia and clonus, loss of superficial abdominal reflexes and extensor toe responses, and eventually atrophy and contracture of muscles, especially hamstrings and calves. Similar disturbances of the motor functions of the head referred to as pseudobulbar palsy resulting from involvement of the corticobulbar part of the pyramidal pathway may lead to spastic dysarthria, dysphagia, impaired strength of mastication and overactive jaw stretch reflex, weakness of the facial muscles, especially the lower, on voluntary effort, with, at the same time, hypermobility of the facial muscles on emotional implementation (lability of emotional expression), and facial muscle hyperreflexia, including a snout reflex and palmomental reflexes.

Interference with control of bladder and bowel function is common in multiple sclerosis. Frequency, urgency and slight incontinence are the earliest bladder symptoms, with progressively greater retentive tendency and more marked incontinence developing later. The loss of control undoubtedly is related to involvement of the efferent suprasegmental pathways in or adjacent to the pyramidal tracts of the cord and to lesions in the posterior columns. The rectal dysfunction is not different from that of the bladder. The outstanding symptom of constipation is analogous to retention of the bladder. It is more common than rectal incontinence only because the more solid content of the rectum leads to greater difficulty of evacuation. If the feces are liquid, rectal incontinence occurs as readily as does that of the bladder.

Involvement of the posterior columns in the spinal cord or their upward continuation through the brain stem to the parietal lobe leads to impairment of position and vibration sense and of discriminative sensibility of the hands. Impairment of recognition of common objects ("dysstereognosis") combined with incoordination of the finer movements leads to a characteristic and severe disability, "the useless hand." An almost pathognomonic symptom of multiple sclerosis, resulting from a plaque involving the posterior columns of the cervical cord, is the occurrence of tingling or electriclike paresthesias extending into the limbs or trunk on flexion of the neck. The spinothalamic pathways of the cord, conducting pain and temperature, are less frequently involved with consequent lesser impairment in these sensory modalities. The descending root of the fifth cranial nerve may be involved with the production of sensory defects on one side of the face or pain resembling trigeminal neuralgia. Pain as a pathophysiologic manifestation in multiple sclerosis is, in general, infrequent, especially in locations other than the face, but it occasionally occurs in a limb or girdling the trunk when a plaque is so located as to irritate the incoming pain fibers of a sensory nerve root.

Involvement of the short fiber pathways of the brain stem is most strikingly manifested by the disruption of function of the posterior longitudinal bundle providing intersegmental integration of eye movements, with the result of dissociation of the conjugate gaze mechanism and the development of nystagmus, which may be vertical (on upward gaze) as well as

horizontal (on lateral gaze). Involvement of the interconnections within the vestibular complex may lead to vertigo. Lesions of the cochlear-trapezoid interconnections for hearing and their upward extension in the suprasegmental pathway for hearing (lateral lemnisci) on rare occasions may produce hearing impairment or severe tinnitus, virtually always bilateral. Pathologic somnolence has on infrequent occasions been noted in multiple sclerosis, presumably related to involvement of the fibers of the reticular substance of the brain stem or of the immediately superjacent hypothalamus. Because of the compactness and heavy traffic of fiber pathways in the brain stem, and a strong predilection for large demyelinating lesions in this region of the central nervous system, it is not surprising that occasionally gray matter becomes involved as a result of spread of the lesion from neighboring white matter. Thus, weakness of ocular or facial muscles more characteristic of segmental dysfunction of gray matter (i.e., lower motor neuron) than of dysfunction of white matter (intersegmental or suprasegmental) is occasionally seen.

Involvement of the cerebellar white matter or connections leads to ataxia of station or gait, intention tremor, and decomposition and incoordination of movement of the limbs. The dyssynergic alteration of speech produced by cerebellar involvement has been referred to as "scanning speech."

Cerebral lesions produce visual as well as motor and sensory defects. Those posteriorly situated in the internal capsule involving the optic radiation may produce homonymous field defects.[37] Similar homonymous visual field defects may occur when lesions develop in the optic tracts or chiasm.[38] The common lesion anterior to the optic chiasm in one or the other optic "nerves" (actually not cranial nerves but extraparenchymal cerebral tracts), referred to as a retrobulbar neuritis, frequently produces unilateral marked impairment of visual acuity with associated central or paracentral scotomas, at times even total blindness (usually unilateral). Though severe visual disturbance is virtually always temporary, residual impairment of vision and the later appearance of pallor of the optic disk are common aftermaths of an attack. Repeated attacks at these sites lead in a minority of patients to permanent near-blindness. That optic neuritis, better termed optic or retrobulbar neuropathy, is caused in the majority of instances by multiple sclerosis, even when unassociated with other neurologic manifestations and even when not followed for years by recurrence, seems well documented.[39-41]

Other cerebral lesions probably involving chiefly the frontal connections with the thalamus, hypothalamus and brain stem give rise to the rather characteristic personality changes and, in later stages, to the mental impairment seen in this disease. Even the pre-illness personality functions in multiple sclerosis have, however, been shown by psychiatric studies to reveal emotional abnormalities, notably immaturity, long before signs of organic disease.[42] Hysterical symptoms preceding or associated with the disease are not infrequently encountered.[43-45]

Euphoria, a benign, cheerful outlook with apparent disregard of physical disability, and with optimism, friendliness and good spirits, is a striking feature in probably the minority of patients and may be a subtle early indicator quite helpful in differential diagnosis. In the experience of most clinicians, however, irritability, querulousness, lack of stamina, emotional instability, and depressive mood tendencies are as characteristic of the earlier stages as is euphoria.[46] These features may give way to euphoria later or persist throughout the duration of the disease, in some instances severely.

Gross impairment of intellectual functions unquestionably is a feature late in the course of the disease in a proportion of patients. The manifestations are decline in interest, concentration and efficiency, loss of memory, and poor judgment, leading in severe cases to a terminal vegetative state. Clinically obvious mental impairment, however, may not occur, since it is dependent on the extent of cerebral involvement, which may be slight. Psychologic investigations of groups of patients including controlled quantitative study of intellectual and affective functions have provided scientific support for these clinical im-

pressions.[47,48] In acute fulminating episodes, of course, massive demyelination of the brain may cause transient stupor with recovery, or even coma leading to death.

Arterial hypotension is an extremely frequent concomitant of multiple sclerosis. Hypertension is rarely or never encountered in association with multiple sclerosis.

Clinical Course

The neurologic symptoms and signs found in patients with multiple sclerosis have already been mentioned in the discussion correlating the structural defects within the central nervous system and the peripheral pathophysiologic manifestations. Such a discussion does not convey a picture of the natural history of the disorder as it affects one patient or another. Because of the variation in acuteness, size, number, location and frequency of occurrence of the lesions, it is obvious that no two patients present the same cross-sectional pattern of neurologic dysfunction or the same longitudinal course of illness. Numerous statistical analyses and summaries have been made of the frequency and temporal relationships of various symptoms and signs, the natural history, course and duration of the disease and of prognostic factors.[3,5,49-54] Though some of these statistical studies have isolated factors in the course of the disease which can be utilized in a predictive or prognostic way in individual patients, the exact course of the disease in any given person is impossible to prognosticate with accuracy.

The duration of the disease may be from a few months to many years. In rare cases an acute fulminating course may lead to death within a period of 6 to 12 weeks. It is in such cases that the differentiation from an attack of acute disseminated encephalomyelitis is difficult. In other patients one sees a fairly rapid downhill course terminating in death in 5 to 10 years. Such patients usually have a number of recurrent, rather severe episodes with intervals of relative recovery during the first few years, but are then left with increasing residua following successive periods of worsening, often not living more than a year or two after becoming bedridden. A third, more chronic pattern in the natural course of multiple sclerosis is characterized by relatively minor attacks of brief duration (days or weeks), separated by asymptomatic intervals of years and followed eventually by slowly and insidiously progressing disabilities. Such a slow, steady course with minor fluctuations eventually leads to some degree of chronic disability after 10 to 20 years but may not materially shorten the life span. In infrequent patients such few widely spaced attacks early in life are never followed by subsequent recurrence or by progressive disability, the disease presumably remaining quiescent throughout the balance of a normal life span. A fifth type of course is characterized by gradually developing motor disability and slow, steady downhill progression, with only slight fluctuations in symptomatology, insufficient to be termed remissions or relapses. Onset later in life is more apt to be followed by this type of course and in general has a poorer prognosis than the remittent type beginning before the age of 25 years.

Thus the disease may last a very short time and be responsible for death in a few weeks to several years; or it may last indefinitely and not shorten the life span at all. Cases are on record in which the disease has been present for 40 to 60 years.[45,55] Attempts to arrive at an average figure for the duration of the disease have little value with such a wide range of duration. Notwithstanding, the average duration of the disease has been computed in various ways from several sets of statistics leading to figures of from 9 to 27 years.[5]

Diagnosis

Laboratory findings—Positive complement-fixation tests utilizing antigens derived from human multiple sclerosis tissues have been reported but their application has not become general.[56-58] Numerous biochemical, hematologic and physiologic abnormalities that occur in most patients with multiple sclerosis are either too nonspecific for use as diagnostic features or involve technics of measurement more suitable for the research laboratory than for the clinical hospital laboratory. Among such are the altered distribution of protein fractions

in the cerebrospinal fluid with a significant increase in the concentration of gamma globulin,[59-62] lowered capillary resistance,[63] an increased blood platelet adhesiveness,[64] occurrence of thrombocyte-agglutinating substance in the cerebrospinal fluid,[65] increased clot retraction time,[66] fluctuation in the number of circulating platelets with fall during active phases followed by rise during improvement,[67] sludge formation in blood vessels,[29] and variations in plasma fibrinogen during the course of multiple sclerosis suggesting an increase during exacerbation.[68] These alterations have not yet served to provide help in diagnosis or understanding of pathogenesis.

The blood count, sedimentation rate and urinalysis (save in the common late complications of secondary infection), routine blood chemistry values, and the bleeding and coagulation times are all within normal range. The cerebrospinal fluid is often entirely normal in multiple sclerosis. Though its content may be abnormal at any stage of the disease, only infrequently does a patient with multiple sclerosis exhibit changes in all the tests that are usually done, namely, cell count, qualitative protein test (Pandy), total protein content, and colloidal gold reaction. Slight to moderate change in one or more of these elements has, however, been reported in 78 per cent of one series analyzed[69] and in 57 per cent of another.[5] The usual order of rise in mononuclear cells, if present, is 5 to 10 per cubic millimeter; rarely it is as high as 50 to 100 cells per cubic millimeter. The usual order of elevation of protein content, if it occurs, is 50 to 60 mg. per hundred milliliters; rarely it is as high as 70 to 100 mg. per cent. The incidence of first-zone colloidal gold curve elevation is probably less than generally thought. Various series have reported colloidal gold changes in from 9 to 80 per cent of cerebrospinal fluids of multiple sclerosis patients, depending on the technic and interpretation. It is likely that by the routine hospital laboratory method about one-third to one-half of spinal fluids of patients with multiple sclerosis will show abnormal colloidal gold precipitation, less than half of these in the first zone. A newer technic of quantitatively standardized gold sol reactions, differentiating curves into seven types, has revealed a 90 per cent incidence of a specific pattern of curve, called "type D," in the fluids of patients with multiple sclerosis.[70,71]

The electroencephalogram is abnormal in roughly half of the patients with multiple sclerosis, but the patterns of irregular rhythm are not specifically diagnostic of the disease.[72] Pneumoencephalograms generally are normal or in later stages show slight asymmetric dilatation of the ventricles and increase in the amount of subarachnoid air over the hemispheres, bespeaking moderate cerebral atrophy. One case of multiple sclerosis has been reported with a transient electroencephalographic focus and ventricular displacement on pneumoencephalography, simulating brain tumor.[72a] Both abnormalities disappeared within three months after subsidence of acute symptoms. Of interest in this patient was a slight rise in pressure of cerebrospinal fluid to 210 mm. and moderate protein elevation to 68 mg. per cent. (The possibility of Schilder's disease or "diffuse sclerosis" of the giant-plaque type, considered by some to be a variant of multiple sclerosis, must always be considered with findings of this type.)

As a laboratory procedure useful in supporting the diagnosis of multiple sclerosis, visual field testing often yields abnormal results in the form of central or paracentral scotomas. A new method of measurement of visual field function in which the threshold of visual flicker-fusion is determined in various fields has been applied to patients with multiple sclerosis.[48,73] This has shown an impairment in flicker-fusion discrimination in the majority of patients with multiple sclerosis even when the visual defects are not revealed by standard field examination. The rare occurrence of homonymous hemianopsia,[37,38] previously mentioned, is another potential visual field finding not inconsistent with the diagnosis of multiple sclerosis, though the finding of central or paracentral scotomas is far more common.

Clinical diagnosis—Diagnosis is made most dependably on the basis of history and neurologic findings. On such clinical grounds it is closely related to the familiar phrase that mul-

ple sclerosis is a disease "scattered in time and space." Two important features weigh heavily in diagnosis: (1) evidence of fluctuations in the course of the disease, either with well-defined remissions and exacerbations or with lesser fluctuations against a background of more or less steady progression, and (2) the elicitation of symptoms and the demonstration of signs indicating scattered lesions in the white matter of the central nervous system.[74]

Differential diagnosis—Because of the variety of symptoms and signs in multiple sclerosis the condition may at a given time resemble any of a number of other diseases of the nervous system. Of considerable importance is the differentiation of multiple sclerosis from surgically remediable conditions such as compression of the spinal cord. This is essential when symptoms or signs are absent above the trunk or neck level, as is the case in occasional patients with multiple sclerosis. Sensory level root pains, partial or complete intraspinal subarachnoid block or jugular compression, and unusually high spinal fluid protein levels are features of intraspinal tumor rarely or never seen in multiple sclerosis. Myelography should always be carried out when these aspects are prominent. Cervical myelopathy associated with spondylosis of the cervical spine (hypertrophic osteoarthritis with degeneration of the intervertebral disk and calcific ridge formation),[75] platybasia, and rare instances of congenital malformations (Arnold-Chiari) are disorders of mechanical origin simulating multiple sclerosis. Assistance in their differentiation is provided by x-rays of the skull and spine, myelography and pneumoencephalography. The older age group in spondylosis, the younger age incidence of the latter two conditions, and the more static course in all three conditions weigh against the diagnosis of multiple sclerosis.

Diffuse degenerative and the more generalized primary demyelinating diseases of the central nervous system can easily be mistaken for multiple sclerosis. Subacute combined degeneration of the spinal cord is identified by the coexistence of primary macrocytic anemia or achlorhydria, signs of peripheral neuropathy, and dramatic response to vitamin B_{12} or liver extract when treated early. The hereditary spinocerebellar degeneration, Friedreich's ataxia, begins far earlier than the majority of cases of multiple sclerosis, presents a more symmetric, diffuse development, and progresses more steadily. The various syndromes of diffuse sclerosis affecting predominantly the subcortical white matter of the brain (Schilder's disease and variants named after Pelizaeus and Merzbacher, Baló, Greenfield, Krabbe, Scholz and others) are characterized by progressive intellectual defects, convulsions, blindness, and ultimate profound mental and physical deterioration. Some of these move rapidly downhill to death and are found commonly in infants, children and juveniles. Others occurring in adults may go on for many years. There is no specific laboratory identification of these disorders, and in the more prolonged states differential diagnosis from multiple sclerosis is difficult during life and must await postmortem examination.

Systemic diseases secondarily affecting the nervous system may transiently mimic multiple sclerosis. In the collagen diseases such as polyarteritis nodosa and lupus erythematosus, fever, increased sedimentation rate, leukocytosis, eosinophilia and visceral involvement (pulmonary, cardiac and renal) usually explain the true nature of the neurologic manifestations. These frequently include painful involvement of muscles and peripheral nerves in contradistinction to the involvement of the central nervous system exclusively in multiple sclerosis. Central lesions, however, producing paraplegia, hemiplegia, diplopia and nystagmus have been infrequently described[76] and may occur before systemic manifestations are severe, thus raising the question of multiple sclerosis.

The blood disorder sicklemia may also produce recurrent symptoms and signs of disseminated involvement of the central nervous system, including vertigo, visual impairment, hemiplegia, cranial nerve dysfunction and sensory defects. The pain, fever, visceral enlargement, anemia and, when looked for, sickling of the erythrocytes provide ready clues to the primary process. The occurrence of repeated attacks of neurologic symptoms and the find-

ing of neurologic signs in young Negroes, especially children, in whom multiple sclerosis is less common, should arouse suspicion of this disorder.[77,78]

Acute disseminated encephalomyelitis, a primary disease of the central nervous system with inflammatory features and prominent widespread demyelination, has for years been considered by some a form of acute multiple sclerosis when not preceded by obvious causally related exanthema or immunization (for smallpox or rabies). In the absence of these predisposing factors, this diagnosis is made in preference to multiple sclerosis when the onset and course are explosive, with fever, headache, at times stiff neck, root pains, and even stupor. Higher cell counts and protein levels in the cerebrospinal fluid merely represent the greater intensity and acuteness of the process and do not reliably differentiate multiple sclerosis from encephalomyelitis. If the patient survives the attack, with or without permanent neurologic sequelae, and subsequent exacerbations or downhill progression does not occur, current practice is to consider the disease encephalomyelitis, probably a hyperergic tissue response related to immunologic factors, rather than multiple sclerosis. The subject has been extensively reviewed and discussed.[79]

Treatment

Predictable curative therapy or dependable preventive measures against multiple sclerosis remain unavailable in the absence of knowledge of specific etiology or mode of pathogenesis. Nevertheless, numerous empiric or semirational methods to counteract the basic disease process are in use. A second category of therapeutic measures are those directed toward symptomatic relief. Lastly, treatment must frequently be applied to the complications of multiple sclerosis.

It has been difficult to interpret the results or to judge the value of specific therapy against the disease because of (1) spontaneous reversibility of symptoms and signs in the earlier course of the disease, (2) irreversibility of symptoms from permanently destroyed, scarred areas of nervous tissue, (3) psychologic peculiarities inherent in patients and their families, often leading to convictions of improvement from almost any mode of therapy, (4) lack of satisfactory criteria for determining cure or even improvement in many instances, (5) obstacles to studying sufficiently large groups of patients over long enough periods to gain statistical validity.

Therapy directed toward the specific disease process will be discussed first, followed by discussion of symptomatic therapy and management of complications.

Primary therapy directed against the disease process—Most of the primary therapies have had as their aim the prevention or counteraction of hypothetical mechanisms of pathogenesis through improvement of circulation to the nervous tissue, enzymatic support of tissue oxidation and metabolic functions, provision of substances to make up for alleged nutritional deficits, interference with possible allergic reactions, or counteraction against possible toxic or infectious agents.

Vasodilators—The basis for vasodilation as a therapeutic method has been the assumption that lesions may be caused by localized areas of vasoconstriction. Histamine by subcutaneous or intravenous administration, as well as by absorption through skin by iontophoresis, has been extensively used but was formerly in greater vogue than at present. No agreement has been reached as to its value. In the favorable reports, the type of improvement has been that which might be expected to occur spontaneously; lasting benefit and material modification of the long-term course of the disease have not been shown. The intravenous injection of tetraethylammonium chloride (TEAC), a sympatholytic agent producing profound vasodilatation and postural hypotension, was given extensive trials in large numbers of patients, intravenously and intramuscularly. Lack of evidence of sustained or long-term improvement has led to discontinuance of this form of therapy. In the past several years a series of clinical investigations on the use of strategically timed acute vasodilation has been reported as showing favorable effects on fresh symptoms or new signs.[80] Agents recommended are amyl nitrite or 5 to

10 per cent carbon dioxide in oxygen (by inhalation) and histamine phosphate (1 per cent) given by iontophoresis until a flush of desired intensity is reached. Such therapies are repeated at variable intervals depending on the course of symptoms. The technics suggested require virtually constant supervision of the patient during acute phases and readiness to apply therapy at a moment's notice throughout the 24 hour period. No confirmation of the favorable results has been published by other workers.

Anticoagulants—The therapeutic effect of the continuous daily oral administration of DICUMAROL® has been reported with favorable and unfavorable conclusions. An early study suggested that in the remittent form of multiple sclerosis it was effective in preventing further relapses.[18] The rationale for anticoagulant therapy in the treatment of multiple sclerosis, based on investigations supporting the occurrence of scattered venular thromboses in the pathogenesis of lesions, has been debated. Because of attendant risks and long-term impracticability, the method has not been generally adopted as a routine treatment for multiple sclerosis.

Nutritional factors and supplements—In former years intensive therapy with liver extract, high doses of vitamins, especially of the B group (orally and parenterally, including intrathecal), was carried out. In more recent years the intramuscular injection of large doses of vitamin B_{12} has been applied. Nicotinic acid in oral, flushing doses continues to be popular. No evidence has been presented that vitamin therapy has been of more than general supportive value in multiple sclerosis. The maximal preservation of a good nutritional state with the aid of a high-caloric, high-vitamin diet continues to be recommended on general principles. Specific vegetable and fruit juice diets proposed in Europe have not come into vogue here. The high-fat diet proposed two decades ago is no longer in use. The results of the more recently proposed low-fat diet in the treatment of multiple sclerosis have been reported as encouraging[28] but this has not been generally confirmed. Because of the possibility that maintenance and function of the myelin sheath may depend on the specific nature of the fatty acid components of the cerebrosides which it contains, and because of a possibly acquired deficiency of such acids, observations were recently made on the feeding of fatty acids from cerebrosides to patients with disseminated sclerosis.[81] No conclusions could be drawn.

Metabolic stimulants—Experimental trials of the administration of adenosinetriphosphate (ATP)[82] and adenosine-5-monophosphate (adenylic acid from muscle)[83] have been carried out. The investigations were inspired by the known importance of these biochemical substances in intracellular chemistry but without certain knowledge of their pharmacodynamic action. The reports suggesting improvement were inconclusive. A study of the effect of the administration of sodium succinate orally and intravenously over prolonged periods revealed subjective and objective improvement in the majority of patients,[84] but the value of this therapy awaits further investigation on a larger number of patients over a longer period. Adrenocorticotropic and adrenocortical hormones have been intensively studied in regard to their therapeutic usefulness and continue to be used in many quarters for the treatment of multiple sclerosis. Discussion of the rationale for the application of these substances will not be attempted in this review. Studies by one group[85] indicated inconsistent results with the conclusion that ACTH and cortisone were not suitable therapeutic agents for multiple sclerosis. Other investigators have also concluded that the value of such therapy was uncertain.[86, 87] However, many clinicians still feel that the immediate use of one of these agents during an acute episode leads to a more rapid defervescence of the lesions and symptoms.

Antiallergic therapy—Though evidence derived from experimental and pathologic studies has suggested that multiple sclerosis might be due to hyperergic tissue reactions in the central nervous system, there is as yet insufficient evidence to indicate that ingestion of foodstuffs or contact with external substances to which the person is hypersensitive plays a role in such reactions. Various measures have

been applied, however, to counteract hypersensitivity, including desensitization injections, after conjunctival and skin testing, and elimination diets.[31] These therapeutic endeavors have not shown sufficiently good results as yet to permit their unqualified recommendation for general use.

Chemotherapy—Over the years many methods of antiinfective therapy have been tried without success. As already indicated, the infectious etiology of multiple sclerosis remains unproved. Recent trials of the empiric application of isonicotinic acid hydrazide (isoniazid) were first reported as giving encouraging results;[88] however, subsequent studies indicated that the treatment was probably not of value.[89,90] Intrathecal tuberculin has been incidentally evaluated in a preliminary study but no final conclusions were reached regarding its therapeutic efficacy.[91]

Miscellaneous therapies—Two studies have reported therapeutic benefit from transfusion of whole blood,[32,92] the rationale for which is given in the respective papers describing the favorable results of therapy. Circulatory stimulants have also been proposed and reported as beneficial in overcoming hypothetical "vasoparalytic" vascular phenomena leading to stasis, sludging and perivascular lesions in the nervous system. For this purpose a variety of vasopressor drugs has been used, inasmuch as vascular hypotension has been found commonly associated with multiple sclerosis. Lack of controls impairs the validity of the impressionistically reported favorable effects.

General measures against the disease process—Several studies have shown psychotherapy to be of probable value in ameliorating the course of the disease as shown by an apparent reduction in the frequency of recurrent episodes and apparent maintenance of a status of lesser disability.[33,42] How this is brought about is unknown, but prevention of possible pathophysiologic alterations secondary to pernicious emotional reactions, e.g., vasoconstriction, has been postulated. General morale-building, supportive psychotherapy as well as more specific psychiatric treatment directed toward specific personality problems and emotional conflicts are often indicated for the well-being of the patient with multiple sclerosis and perhaps may eventually have more specific value if factors of life stress and attendant emotional factors contribute to pathogenesis. As a background for any other measures of therapy that are directed toward the patient, the physician should demonstrate willingness to care for the multiple sclerosis sufferer and to preserve an optimistic attitude.

Because first attacks and new episodes seem often to follow physical strain, exhaustion or chilling, the avoidance of these situations, limited programs of activity commensurate with the patient's capacity and tolerance during static or steadily progressive phases, and prolonged rest following new episodes are in all probability helpful in preserving optimal control over the course of the disease. Vigorous treatment of coexistent or intercurrent infections, including bed rest, may diminish the possible risk of worsening the disease or precipitating a relapse. It is doubtful whether moving to a warmer climate is of specific value in modifying the course of the disease except as it represents opportunity for rest and freedom from stresses inherent in the patient's usual situation. Reference already has been made to preservation of optimal nutrition by means of a generally well-balanced, high-caloric, high-vitamin diet.

Operations and general anesthesia, if elective and not absolutely essential, are best avoided but should not be contraindicated if necessary to the patient's well-being. Certain types of anesthesia, such as spinal and perhaps inhalation with ether, may have an aggravating effect. The long-held notion of a deleterious effect of pregnancy on the course of the disease has been cast into doubt by recent statistical studies. On the basis of these, pregnancy would not appear to be contraindicated unless the emotional or physical stresses consequent on subsequent rearing of the child are great. It is doubtful that pregnancy should ever be interrupted because of multiple sclerosis save where vital functions of the mother are threatened by the advanced state of incapacitation, including pseudobulbar palsy.

Symptomatic therapy—Symptomatic therapy is the most important aspect of the man-

agement of patients with multiple sclerosis.

Motor dysfunction—The motor loss in multiple sclerosis consists of weakness, muscle wasting, loss of functional patterns, ataxia, intention tremor, impairment of fine skilled acts, spasticity, involuntary reflex spasms, and muscle contractures which restrict full range of motion at the joints. Technics of physical therapy, developed to counteract all these phenomena, may in some cases be used to advantage. In addition, drugs are coming into use which show increased effectiveness in counteracting spasticity and reflex spasms. Physical therapy is of no value for the nonmotor symptoms of multiple sclerosis (visual, speech, sensory, bladder, etc.). It is probably contraindicated in acute phases of the disease where rest would appear to favor reparative processes in the central nervous system. In those cases where a slow, steady downhill progression is evident, it may assist in slowing the rate of progressive incapacitation. Its maximal usefulness appears to be in those patients who have residual motor disabilities but are in a relatively static phase of the disease. Here, active resistance exercises to improve power of limb and trunk muscles, daily passive stretching to counteract spasticity in order to delay inevitable contracture, and coordination exercises are helpful. Gait training, to improve efficiency and safety, and help in learning new ways of achieving the innumerable daily acts of living are of special importance in increasing the independence of such patients.

Drugs to reduce spasticity and reflex spasms continue to be evaluated. Mephenesin (TOLSEROL®) and curare are but little used for this purpose now. Chlorpromazine (THORAZINE®) and meprobamate (EQUANIL®, MILTOWN®) have been shown to have slight muscle-relaxing properties on oral administration. The most recently developed synthetic oral skeletal-muscle relaxants, zoxazolamine (FLEXIN®), methocarbamol (ROBAXIN®), chlorzoxazone (PARAFLEX®), and carisoprodol (SOMA®), appear in some patients to have a fair effect in reducing spasticity and flexor spasms, but as yet no ideal agent for this purpose is available.

When spasticity is extremely severe, with hyperadduction and scissoring of the lower limbs, excessive involuntary flexion spasm, and beginning deformity due to incipient contractures, the likelihood of ever regaining useful function of the lower limbs is remote. In such instances, as a measure of last resort for symptomatic help, surgical intervention is carried out. This may be selective alcohol block (or surgical section) of the sciatic nerve or lumbosacral nerve roots to bring about permanent relaxation of lower limb muscles. Such procedures usually add greatly to the patient's comfort and alleviate nursing problems, though permanent paralysis of the denervated muscle groups must be accepted.

Bladder and rectal dysfunction—The lesser degrees of bladder dysfunction such as urgency, frequency and occasional mild incontinence may be effectively relieved through the use of anticholinergic drugs including the belladonna alkaloids, especially atropine, and the synthetic preparations such as propantheline (PROBANTHĪNE®) and isopropamide (Darbid). Though fecal incontinence is less common than urinary incontinence, these drugs similarly inhibit involuntary rectal overactivity. The more common rectal symptom of constipation has been effectively treated by use of an oral detergent, dioctyl sodium sulfosuccinate (DOXINATE®, COLACE®), and mild peristaltic stimulants such as senna derivatives (SENOKOT®) or cascara. Another preparation sold commercially for the latter purpose is 1,8-dihydroxyanthraquinone (DORBANE®). Many patients are able to establish quite regular bowel habits with spontaneous evacuations every second or third day through the help of these agents. In other patients regular bowel emptying is impossible save with the use of regularly given enemas, usually not more often than at two or three day intervals.

In patients with more advanced disease who have total loss of bladder control, an indwelling catheter is essential to counteract the damaging effects of chronic urinary retention. The catheter may be attached to a tidal drainage apparatus, providing rhythmic and somewhat more physiologic filling and emptying of the bladder, or simply to a dependent rubber drainage tube leading to a reservoir. Rubber urinals strapped to the thigh or leg are quite

useful and practical for this purpose if the patient is ambulatory or in a wheel chair. Complications in relation to bladder disturbances are discussed later.

Patients frequently seek symptomatic help for visual disturbances. The impairment of visual acuity due to retrobulbar neuritis cannot be symptomatically helped and patients should be discouraged from seeking repeated refractions and changes of lenses. Diplopia, present as long as both eyes are open, may be eliminated by using a plastic eye shield alternately covering one eye or the other.

Some patients with multiple sclerosis are euphoric and apparently in little emotional distress. Others, however, seem perpetually irritable, dissatisfied, tense, apprehensive or depressed. The long-term use of one of the newer ataractics is justified if an ameliorating effect on the emotional disturbance can be demonstrated by trial of one of these agents. Chlorpromazine (Thorazine) or one of the monoamine oxidase inhibitors (MARSILID®, NIAMID®) may lead to sustained improvement when anxiety on the one hand or marked depressive features on the other are prominent. It should be borne in mind that aside from providing comfort and operating as a symptomatic measure, it is possible that the relieving of pernicious emotional states may be of benefit to the specific disease process itself.

Treatment of complications—The complications of bladder dysfunction are those of secondary infection, formation of bladder calculi, and obstruction of bladder drainage from encrustation of the catheter. Prevention of these complications may be assisted through daily irrigation of the bladder with 180 to 240 cc. of 0.5 per cent acetic acid, liberal intake of liquids, substitution of clean sterile catheters at intervals, and the daily administration of an antacid such as a colloidal aluminum gel, claimed to inhibit the excretion of phosphates in the urine. If there is no encrustation of the catheter and no evidence of acute infection, the catheter may be left in place indefinitely. Regular urinalysis to determine the degree of inevitable pyuria, and culture of the urine when there is systemic or local evidence of an acute flare-up of genitourinary tract infection should be carried out, followed by treatment with appropriate chemotherapeutic and antibiotic agents when indicated. These should never be given over a long period or used prophylactically.[93] As a long-term preventive measure, the use of methionine by mouth for urinary antisepsis has been shown to be of value.[94]

When patients are chair-ridden or bedridden, decubitus ulcers sooner or later become a problem and should be treated by the usual conservative measures which will often lead to healing. These are avoidance of further pressure, application of wet dressings, antibiotic solutions or ointments, or, in some instances, simply exposure to air or heat lamp followed by dry sterile dressings. If necessary, unless the patient is virtually moribund, surgical repair should be carried out, including debridement and grafting.

Though pain is an infrequent symptom in multiple sclerosis, the occasional occurrence of facial pain resembling trigeminal neuralgia demands help. High doses of orally administered nicotinic acid (100 to 200 mg. four times a day) seem in some instances to be associated with relief of the paroxysms. The response of this symptom to high doses of vitamin B_{12} parenterally has been quite as inconsistent as has been the response of other symptoms of multiple sclerosis. Sodium diphenylhydantoin (DILANTIN®) in the usual dosage (0.1 gm. three or four times a day), recently shown to be of value in tic douloureux, may be effective in paroxysmal facial pain in multiple sclerosis. Peripheral alcohol block of the involved trigeminal division as a temporary measure followed by eventual trigeminal root section has been resorted to when pain was persistent and recurrent. Why this should be helpful is unclear.

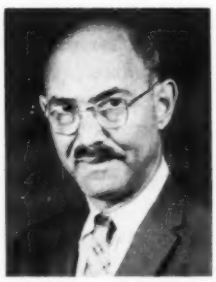
The complication of acute pulmonary infection is treated in the usual way. In patients with far-advanced multiple sclerosis, aspiration pneumonia or hypostatic pneumonia may be a terminal event regardless of therapy.

The references accompanying this article will be included in the author's reprints and may be obtained on request to the Editorial Department, POSTGRADUATE MEDICINE, Essex Building, Minneapolis 3, Minnesota.

The Electroencephalogram in General Practice

ROBERT S. SCHWAB*

Harvard Medical School, Boston



ROBERT S. SCHWAB

An electroencephalogram generally gives the most information if it is interpreted by a neurologist or someone trained in neurology or neurosurgery who has a chance to examine the patient in consultation and to integrate the tracing with the neurologic findings and history. When the general practitioner himself must integrate these findings, he must know something about electroencephalography, the indications for its use, what the abnormalities might mean, and what the chances are that the record might be improperly interpreted. When in doubt, it is best to check with a neurologist by telephone to see whether or not the tracing is consistent or reasonable in view of the other findings.

THE electroencephalogram may be defined as a 30 to 60 minute measurement of the electric activity of the brain obtained from electrodes attached to the scalp. The records, as they usually appear, consist of several wavy ink lines which represent the electric changes in the wave forms from pairs of electrodes, each pair representing one line. There usually are eight separate units or channels doing the recording at the same time, and many modern laboratories may use 16 individual recorders.

The speed of the recording paper is a little faster than that of the usual electrocardiogram, which is 2.5 cm. per second or nearly an inch. The speed of the paper for electroencephalography is 3 cm. or about 1¼ in. per second. The voltage of the normal human brain wave as recorded between two electrodes on the scalp is somewhere between 25 millionths of a volt and 100 millionths of a volt or 100 microvolts, which is the term usually used. As in many of the modern electrocardiographic instruments, vacuum tube amplifiers are used, so that these feeble voltages are increased in size several million times until

*Assistant Clinical Professor in Neurology, Harvard Medical School; Director, Electroencephalographic Laboratory, Massachusetts General Hospital, Boston, Massachusetts.

they are powerful enough to move a recording pen, usually carrying ink, back and forth, corresponding to the original wave formation.

Brief Historical Note

In the latter part of the nineteenth century a great many scientists recorded electric changes from the exposed brains of animals. The most noteworthy of these scientists was Caton of England, who reported his findings in 1875. Shortly after World War I, vacuum tube amplifiers and better recording apparatus were made available to scientists, and in 1926 Dr. Hans Berger in Jena, Germany, began to record the electric waves in human beings from the scalp. He published his first report of these observations in 1929. He is regarded as the father of human clinical electroencephalography. From that date on, many different scientists in various parts of the world confirmed Berger's findings of waves from the brain. Professor E. D. Adrian in Cambridge, England, was the first to report these confirmatory observations in English, in 1933. In the United States, Drs. Herbert Jasper, Frederic Gibbs and Hallowel Davis are the pioneer workers in this field. They described electroencephalograms in normal human beings and in those with epilepsy in 1934 and 1935. From this point on, laboratories were started in nearly every large city in the United States and abroad, and at present there are adequate laboratories throughout the country. These include a large number of private ones, usually in charge of a neurologist, psychiatrist or neurosurgeon, so that there are few places where the general practitioner does not have an opportunity to get these tests done if he decides they are indicated.

Interpretation of the Tracings

At this point, something should be said about interpretation of the tracings as they come from the apparatus. The apparatus has been standardized and there are a number of reliable manufacturers who produce them and keep them repaired, so that in a sense they have the reliability of x-ray equipment. It takes an intelligent young lady approximately six months to learn how to obtain the records from such an apparatus when she is properly instructed in a laboratory with experienced workers. It also takes a well-trained physician, usually someone with neurologic training, from six months to a year of supervised experience and instruction to learn to interpret these tracings in a reliable and satisfactory manner. Many physicians who would like to interpret these records, and who have an opportunity to set up such a laboratory, do not have the time or the inclination to spend such a full period of training. As in any field of medicine, an inadequately trained person may continue to turn out inaccurate, unreliable, inconsistent reports for many years. One can deplore such a situation when it exists, but there is little anyone can do about it except hope that more experienced people will enter this field as its importance continues to grow.

Procedure

The procedure itself is painless. The patient does not require any special preparation and comes to the laboratory having been reassured that it will not hurt, that the hair on the head will not have to be taken off, and that the procedure will last somewhere around an hour. In most recordings, the patient either sits in a comfortable chair in a semireclining posture or lies on an examining table or bed with his head on a pillow.

The electrodes are fastened to the various areas of the scalp by an adhesive-type conducting paste in most instances, or sometimes a sharp No. 26 needle is quickly and painlessly put in the subcutaneous area of the scalp over the appropriate place and serves as an electrode. In Europe, various types of elastic helmets are used, and the electrodes are held in place under these by elastic strips, but this technic is not very popular in the United States.

From 10 to 25 electrodes are placed on the scalp for an ordinary recording, arranged symmetrically so that the same number is over each hemisphere of the brain. Standard placement adopted by the International Federation of Electroencephalographic Societies and used in approximately half of the laboratories in the world follows the "ten and twenty system." A line is drawn from the nasion to the

occipital protuberance, and this line is broken up into six spaces, the first being 10 per cent, the next four being 20 per cent, and the final 10 per cent being the space between the last occipital electrode and the occipital protuberance. These measurements are not difficult and they do give a consistency toward international standards. Other laboratories achieve approximately the same positioning by bisecting these lines and cutting the half measurements into thirds by eye. It does not make a tremendous amount of difference if there is a variance in the electrode placements of ¼ or ½ in. compared with those used in other laboratories provided one understands the limitations of localization with this technic. The important thing is that the right side of the scalp should be covered with electrodes in exactly the same way as the left. It is usual for the electrodes on the left side of the head to have odd numbers, and those on the right side even numbers. The midline electrodes use the highest numbers on the electrode board that hangs by the patient's head.

The recording itself takes approximately 40 minutes. The patient usually is asked to close his eyes and relax. The various points of the head are lined up on the apparatus. Calibration similar to that in electrocardiography is used first. The technician is careful to see that the various separate amplifying units are responding in an identical manner.

To designate a brain wave as normal requires information as to whether the subject is drowsy or alert or asleep, since these states alter the characteristics. Therefore, the usual electroencephalogram is taken with the subject relaxed but awake and alert, not under the influence of drugs, not fasting, with normal blood sugar, and breathing in the usual way at a rate of around 18 breaths per minute.

Brain-wave Frequencies

It might be well to mention the frequencies in the brain wave that are used in the reports. The fastest are between 18 and 30 per second and are called beta waves. These usually are found around the frontal regions of the brain when recorded through the scalp and have voltages of between 20 and 40 millionths of a volt. Over the parietal or occipital areas there are rhythms that are slower than the beta, namely, alpha, which run from 8 to 13 per second, have a regular sinusoidal appearance and have a voltage of between 20 and 80 millionths of a volt.

The abnormal rhythms consist of higher voltages than normal in both the beta and alpha frequencies. There is an intermediate fast abnormal frequency around 12 to 14 per second. There is an abnormal frequency just below the alpha band, namely, four to seven per second, and when it comes from the temporal areas it is called theta activity. A still slower frequency, called delta, from one and one-half to three and one-half per second, is found over areas where there is abnormal brain tissue and is therefore an abnormal frequency. All these observations assume that the patient is not asleep and that he is an adult (approximately 17 years or older).

From infancy to the age of around 14 years, the frequencies that are normal are progressively faster as one gets older, so that in an infant three-per-second waves are considered within normal range. The alpha rhythm of a seven year old child is around eight per second. These changes with age are difficult to interpret when compared with the findings in adults—and indeed the pediatrician who has to handle electroencephalographic reports has a more difficult time than does a physician whose patients are adults. The same thing is true of geriatric patients over the age of 65 years. Here the normal rhythms begin to slow down a bit as one goes into the seventh and eighth decades of life. A seven-per-second alpha rhythm in a 90 year old subject is probably well within normal range.

In general, abnormality in the brain wave can be diffuse, all over the head; intermittent, normal for a few seconds and then abnormal; paroxysmal, normal for some time and then suddenly displaying a burst of abnormal activity, followed by a normal wave; focal, in one area only, and lateralized in one hemisphere only; or a mixture of two or more of the types just mentioned. These various types of abnormality as well as the two kinds of normal waves that have been described indicate

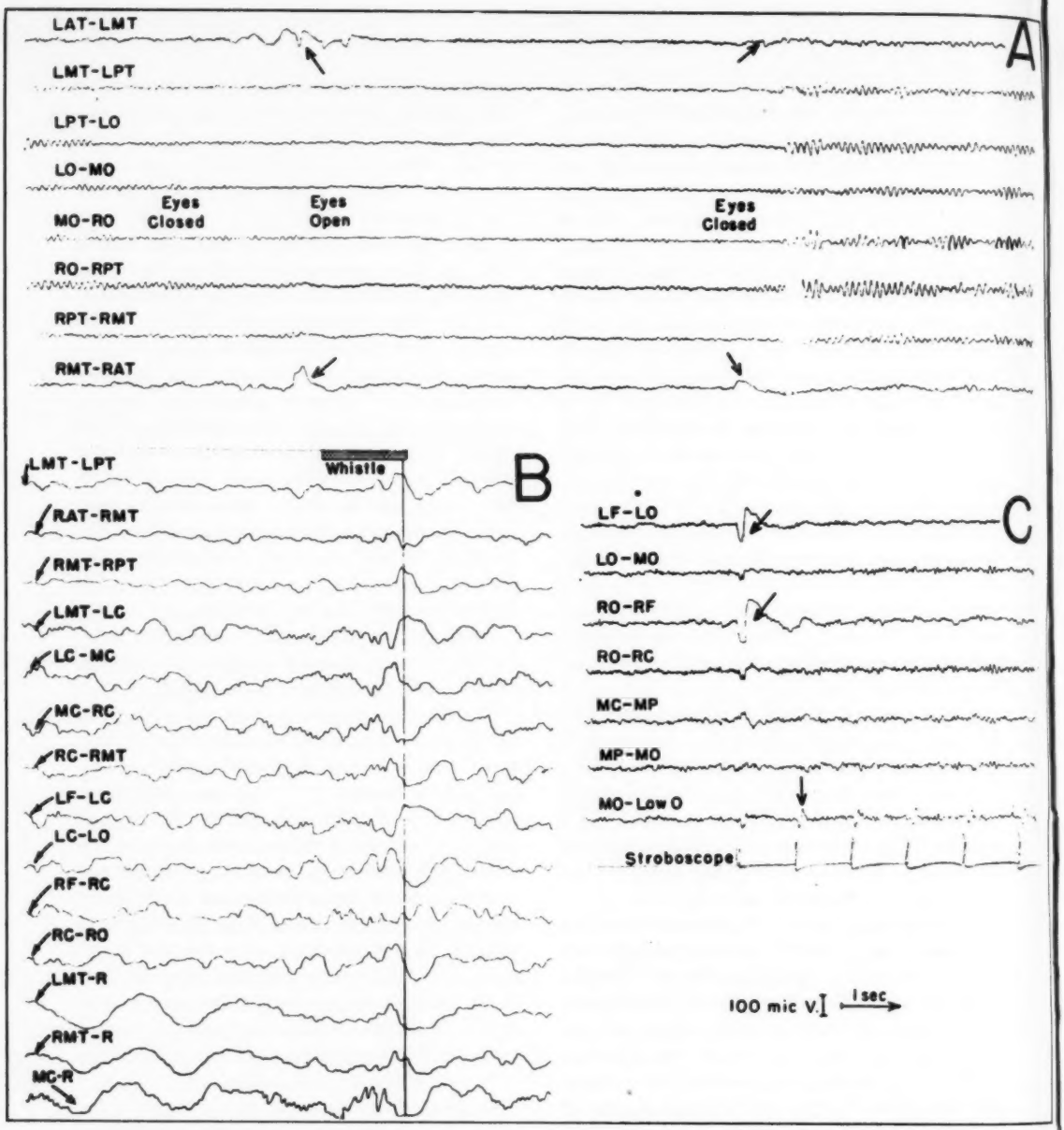
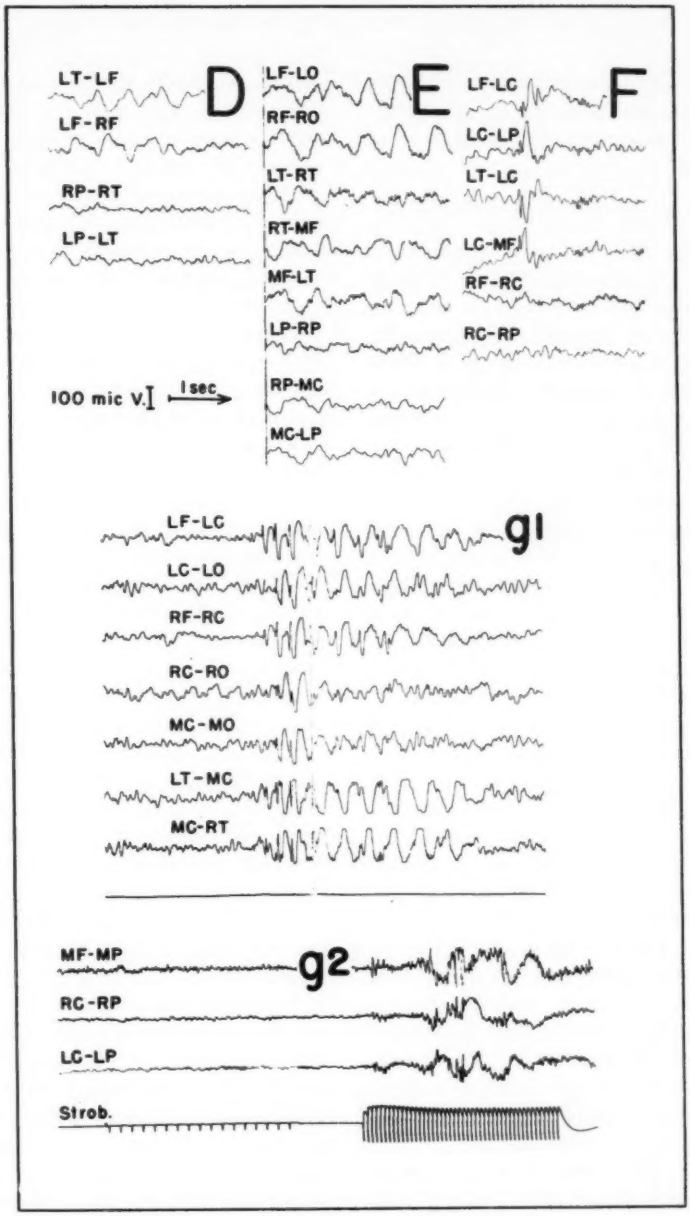


FIGURE 1. Abbreviations used in illustrations: R—right; L—left; F—frontal; C—central (motor area); T—temporal; P—parietal; O—occipital; A—anterior; M—mid; R—reference or inactive lead, e.g., nose, both ears or midpost neck; mic V.—microvolt; sec—second; Strob.—stroboscope.

A. Eight channel record of normal subject with eyes open and closed. Note symmetry on the two sides and disappearance of alpha when eyes are open. Arrows show an artefact in the anterior temporal region from eye movement.

B. A strip of 15 channel recording of the subject asleep. Note slow waves, absence of normal alpha, and symmetry on the two sides. Block on first line shows whistle and evoked response in all leads at line. Small arrows indicate the channel for each pair of electrodes.

C. Normal subject, showing flash in eye and evoked response in the occipital area which is seen only in the low occipital lead. Arrows show eye movement in frontal leads.



D. Abnormal subject; brain tumor. Left frontal region, showing slow delta waves.

E. Abnormal subject; head injury. Shows slow three per second delta and five per second theta on both sides.

F. Abnormal subject; epilepsy (seizure pattern). Focal-type epilepsy with spike and slow-wave focus occurring spontaneously in left temporal region.

G. Abnormal subject; epilepsy (seizure pattern). (1) Petit mal-type epilepsy, showing three per second spike and wave, activated by overbreathing. (2) Myoclonic jerk and short seizure, activated by 15 per second stroboscopic flash, but not by five per second flash.

(Reproduced from HARRISON, T. R., ADAMS, R. D., BENNETT, I. L., JR., RESNIK, W. H., THORN, G. W. and WINTROBE, M. M. (EDS.): Principles of Internal Medicine. Ed. 3. New York, McGraw-Hill Book Company, Inc., 1958, p. 497.)

that interpretation of the tracing is not as easy as one might suppose from the fact that there are only two kinds of normal rhythms, the rest being abnormal.

Indications for Electroencephalography

The most obvious indication for electroencephalography is a situation where one would expect that the record would assist in establishing a diagnosis. Epilepsy is perhaps the most important condition from this standpoint. Epilepsy is a paroxysmal behavior pattern involving motor behavior, peculiar sensations and disturbance of consciousness and is accompanied in almost every case by a discharge in the electroencephalogram during the epileptic seizure. Brief seizures of the petit mal type, lasting only 5 to 15 seconds, always are associated with a characteristic mixed pattern of abnormality, a slow wave and a sharp or spike wave called a wave-and-spike occurring at three per second, all over the head and of high voltage. When it appears, it is so characteristic that one feels a diagnosis can be made from the recording alone. Even this, however, is not safe, because a certain number of relatives of epileptic persons, relatives who have never had clinical seizures, may have very short one-to-two-second bursts of these spikes and waves without any clinically measurable seizure activity. About 75 per cent of epileptic patients will have some kind of abnormality even when they are not having a seizure; this is the "inter seizure" record, but this abnormality is *not* specific for epilepsy. It is simply an abnormality and should lead one to make the diagnosis when it is integrated with other clinical findings obtained in examinations and from the history.

Injuries to the brain that occur as a result of automobile accidents or other trauma to the head invariably produce disturbance in the electric rhythms, particularly over the bruised, contused or lacerated area. If there is simply a bump on the head with a scalp laceration, or a contusion of the scalp without actual damage to the brain, the electroencephalogram will be perfectly normal, and this is reassuring to both physician and patient. More severe injuries to the head will result in generalized, focal or lateralized abnormality, more conspicuous right after the injury but gradually improving until at the end of three to six months the record is usually normal again. Thus, electroencephalography is a rather useful way of following the progress of a head injury when the tracings are integrated with the clinical findings, history, x-rays, and so on.

A cerebral vascular accident such as thrombosis of one of the major vessels on one side of the brain will produce an abnormality at the time that it occurs—a focal abnormality—but as the edema subsides, even though motor power does not return, the electroencephalogram may become normal. In a certain number of cerebral vascular situations the abnormality persists, and this is some indication that the vessels which have been thrombosed and have not recovered are located near the surface of the cortex rather than deep in the white matter.

Space-occupying lesions such as subdural hematomas, brain abscesses, brain tumors or intracerebral clots of blood will produce focal electroencephalographic abnormalities which persist. These space-occupying lesions do not disappear, and the abnormality usually gets worse over the months, and therefore an electroencephalographic record that is deteriorating from a moderate degree of abnormality to a severe degree of abnormality is very suggestive that there is some space-occupying lesion present.

The foregoing indicates that the most useful way to employ electroencephalograms in clinical practice is to make a number of tracings for the same patient at intervals. These serial records will indicate the progress of the abnormality. Improvement of the tracing usually coincides with clinical improvement, but worsening indicates that something serious is taking place within the cranial cavity.

Integration of Electroencephalographic Findings With Clinical Picture and History

In general, it would seem that the electroencephalogram interpreted by a neurologist or someone trained in neurology or neurosurgery would give the most information to the refer-

ring general practitioner if this same neurologist, neurosurgeon or psychiatrist had a chance to examine the patient in consultation. He could then integrate the findings of the electroencephalogram with his own neurologic findings and the neurologic history. This often is not possible, and sometimes would complicate the patient's economic load unnecessarily, so that the report has to be integrated in many situations by the general practitioner himself, with his knowledge of the patient's clinical state.

If this is the case, the referring general practitioner must know something about the electroencephalogram, in what conditions it should be ordered, how often it should be ordered, what the abnormalities might mean, and what the chances are that the record might be improperly interpreted through an inexperienced person in the laboratory. This is a very difficult situation, and when in doubt the best thing to do is to consult a neurologist by telephone, describe the report that you have before you and the state of the patient, and ask him whether this is consistent or reasonable in view of the findings that you have recorded. In something like 75 per cent of the cases, the report that you will get from the laboratory will fit your own knowledge of the patient's clinical state. If the findings are normal, you will be reassured that the brain is functioning in a normal way, and there will be no need for going further. If the record is clearly abnormal, it may help to lead you to consult a neurologist or neurosurgeon or to admit your patient to a hospital for further study, which may involve arteriography or pneumoencephalography or even surgical exploration.

Postgraduate Clinical NOTES

139. FAULTY DIET AND CARDIAC INFARCTION

The common belief is that there is a simple progression, leading directly from faulty diet to cardiac infarction. It is said that, in the wealthier countries, many diets have excessive amounts of saturated fats and deficient amounts of unsaturated fats. The result is an abnormally high level of cholesterol in the blood. This leads to atheroma. The coronary arteries consequently tend to become narrowed and finally occluded, either by the atheroma itself or by a blood clot.

It is now clear that such a simple hypothesis cannot be sustained. Of the various steps of dietary fat to cardiac infarction, it is only the first which is fairly definitely established. Consumption of saturated fats raises blood cholesterol; consumption of unsaturated fats lowers it. As to the second step in the hypothesis, we can say very categorically that high blood cholesterol does not necessarily mean increased atheroma. Moreover, this lack of correlation extends back to dietary fat. The South African Bantu, with a low intake of fat and a low level of blood cholesterol, does not seem to have less atheroma than the European. The third step in the progression, that atheroma will lead to cardiac infarction, has also not been established. In Great Britain there has been a considerable increase in mortality due to cardiac infarction, but there does not appear to have been an increase in the incidence or degree of atheroma.

John Yudkin, Etiology of cardiac infarction, *A.M.A. Archives of Internal Medicine*, December 1959, pp. 681-683

Diagnosis and Treatment of Schizophrenia

ROBERT A. COHEN*

National Institutes of Health, Bethesda

Diagnosis of schizophrenia is within the province of the clinician. It rests chiefly on the history and observed behavior of the patient, on his responses to the physician, and on the feelings he evokes in the trained observer.

Therapeutic principles are derived naturally from understanding the schizophrenic person's experience in the world about him. Success in treating schizophrenia depends on understanding the patient's psychologic and social status and on the skillful administration of drugs and other therapy.

ROBERT A. COHEN

No matter what his special field of interest, everyone engaged in the practice of medicine sooner or later will come into contact with a schizophrenic individual. Once the diagnosis is established, particularly in those instances in which the emotional disturbance becomes progressively more severe, it may be well to turn to the psychiatrist for intensive therapy. However, the general practitioner, especially if he is the family physician, is often in a position to tilt the scales in the direction of a favorable outcome, not only because of his close relationship with the patient and the family but also because the time at which he is consulted is likely to be a crucial one in the acutely developing phase of the illness.

The diagnosis of schizophrenia still remains within the province of the clinician. Efforts such as that of Akerfeldt[1] to develop a biochemical test which would establish the diagnosis entirely by objective means have thus far proved unsuccessful. Similarly, projective psychologic tests such as the Rorschach and the thematic apperception tests, subject as they are to individual interpretation, have contributed only modest new dimensions to the methods of clinical evaluation. Diagnosis still

*Director of Clinical Investigations, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland.

rests mainly on the history and the observed behavior of the patient, on his responses to the physician during examination, and on the inner feelings the patient evokes in the trained observer.

In this short article no attempt will be made to list the various types of schizophrenia. The official nomenclature[2] describes these in adequate detail. They are more exhaustively considered in the monographs of Kraepelin[3] and of Bleuler[4] and in the two encyclopedic reviews edited by Bellak.[5,6] With full knowledge that reliable generalizations cannot be made in this field, since there are substantial reasons to doubt the etiologic and dynamic homogeneity of what is called schizophrenia, an effort will be made to convey something of the nature of the schizophrenic person's experience in the world about him. Principles of therapy derive naturally from such an understanding.

The Schizophrenic State

First, it must be pointed out that the schizophrenic state is not continuous. There may be lengthy intervals during which the patient is clear and lucid, and this fact may lead to an underestimation of the seriousness of the situation. Conversely, the patient may appear completely unintelligible and out of contact; this may lead to a premature pessimism and a turning away from him in unwarranted despair.

The essential psychologic process which seems to be involved in schizophrenia is a defect in the power to inhibit and, therefore, to order internal and external stimuli. The boundary between the self and the outside world shifts or it may even disappear altogether.[7,8] In this sense it is, perhaps, not unlike an infant's earliest experiences in the world. There is no capacity to discriminate between what is relevant and what is irrelevant in the mass of stimuli which impinge on one. Consequently, there is lack of clarity as to which action might reach a goal.

Since the schizophrenic patient has difficulty in deciding whether a thought or a feeling arises from within or in response to a stimulus from his environment, conventional cause-and-effect thinking disappears. There may be terrifying feelings of vastness and littleness. He feels caught in a situation of cosmic threat, as if he and the world in which he lives might disintegrate and melt away into nothingness. Things which formerly had no meaning assume the greatest significance; the casual gesture, the arrangement of articles of furniture, and the adventitious sound all convey a message and may serve, for example, to modify or even negate what was meant to be a word of sympathy or encouragement. Thought and language become highly autistic; actions and words no longer convey their common meaning. A nationwide television program is put on to inform one patient of his friend's unfaithfulness. A schizophrenic girl consults an ophthalmologist; she does not tell him she wants her eyes examined because people seem to grow larger and smaller as she looks at them. When told her vision is normal, she becomes more overtly disturbed. A young man goes to the telephone company office to ask whether a sanatorium is a hospital or a hotel. A nurse had refused to interrupt a card game with another patient when he asked her for an aspirin, and in this indirect way he dealt with almost murderous rage which he feared might drive him to violence. An unhappily married woman shoots and kills a resident physician who had been unusually kind and thoughtful in treating her at the time her child was born; only in this manner could she get him out of her mind.

Like all schizophrenic behavior, the vignettes cited reflect both the disturbing stimulus and one effort the patient has made to deal with it. When all such efforts fail or lead to disaster, a gradual breakup of the personality occurs and the classic textbook picture of schizophrenia supervenes. However, even these grossly psychotic symptoms can be understood as desperate attempts to identify a possible source and ameliorate a feeling of overwhelming anxiety and of the imminent dissolution of the self.

This cursory description of the psychologic experiences of the schizophrenic individual has been presented because many of the evils which follow the appearance of the syndrome come from the patient's interactions with those

who are ostensibly trying to help him. This view of the psychologic importance of the attitudes of the therapeutic personnel would be accepted by many who hold to a physiologic etiology as well as by those who stress psychologic and social factors. No patient is in greater need of understanding; in no other circumstances is it more important to practice the art as well as the science of medicine.

The floridly schizophrenic patient characteristically induces intense distress in those about him. One feels the greatest discomfort, a desire to get away, to correct the patient, to do something—anything to get out of this vaguely defined but thoroughly uncomfortable situation. Instead of listening carefully and at length to the patient, or even scrutinizing one's own feelings in an effort to identify if possible the source of the discomfort, one is all too frequently impelled to ignore the patient in the hasty pursuit of one's own emotional security. As Dr. J. Cumming pointed out, while the patient is still regarded as sick, he is treated with sympathy, consideration and respect. As soon as a diagnosis of psychosis is made, people shrink from him and speak evasively or even untruthfully in their fear of his losing control. All this serves to intensify the patient's confusion, and it may be further compounded if it is necessary to remove him from the familiar settings of his home and his work and commit him to a large mental hospital. There, with little or no privacy, with his clothing taken away and replaced by a hospital gown, with nurses and doctors so overburdened that it is difficult for them even to learn to recognize him by name, many of the usual props of normal everyday life are missing and the patient's feeling of living in a nightmarish world often may be accentuated.

Treatment

When one reviews the literature relating to the therapy of schizophrenia, one is immediately impressed by the vast number of antithetic and incompatible approaches which have been advanced as effective in the hands of their individual proponents. These range from lobotomy, colectomy and castration through the search for and eradication of every conceivable focus of infection, through insulin and electroshock therapy, through the use of sedatives and ataractic drugs to the various types of psychologic treatment. At one time or another each has been employed with enthusiasm and effect by the profession; but, despite some real advances in our knowledge, schizophrenia remains with us, and mental patients still occupy more than half of all hospital beds.

In this paper, reference will be made only to the phrenotropic drugs and to psychotherapy. Insulin and electroshock therapy are properly within the exclusive province of the specialist. The drugs show promise both for treatment and for greatly increasing our knowledge of the biologic bases of behavior. However, it also should be clear from the foregoing that one should not prescribe a pill for the schizophrenic patient and then pass on to the next case; a human being under such stress is in need of some personal attention as well.

I have dwelt at length on the nature of the schizophrenic experience because I believe that it is not possible to prescribe an attitude or a bedside manner. Each of us varies his approach to the individual patients in our practices in accordance with our understanding of the type of person the patient is and in accordance with our own way of dealing with that particular type. With one patient we may be quiet, serious and reserved; with another, somewhat more talkative and reassuring. For one we may prescribe firmly and authoritatively; with another, we may explain our procedures at some length and enlist his cooperation. If a patient has a fractured femur, our psychologic approach is perhaps of little importance compared with our skill in reducing the fracture and setting the bone. With schizophrenic persons, one's understanding and attitude are of the essence, particularly in the early acute stage, when it is often possible to bring about a dramatic reversal of symptoms.[9] Conversely, the opportunity to contribute to the solidification of the schizophrenic state is equally great.

Although specific directions cannot be given, there are some general rules one can

follow. It is important to realize that even the most disturbed patient will at least occasionally say something that is illuminating and important. This should be noted for eventual use but not responded to immediately, because the schizophrenic individual often employs conventional terms in a private manner. For example, when in response to a patient's question, a physician stated that he liked the patient's blue shirt, this was interpreted as a desire for a homosexual relationship. Usually, by listening to the context, one can get some idea of whether or not the patient's statement was simple and direct. When one does not understand, it is well to say so; when one does, it is useful to let the patient know.

Generally speaking, the goal of the psychologic aspect of the approach to the patient is to do what one can by such means to allay his panic and to promote his regaining a sense of distance between himself and the world about him. The task is to establish and maintain contact and communication, not to tell him what is wrong with him. The usual medical stereotype of "offering help" is often experienced by the patient as an attempt to take him over, body and soul, and it may result in an exacerbation of his psychotic behavior. The patient needs more to be understood than to be helped. If the physician says, "Let's see what we can make out of this," he implies a readiness to work with the patient toward an understanding of the situation. "I want to help you" may convey to the patient a feeling that the physician regards himself as superior and wants to dominate him. The goal is the creation of an atmosphere in which the physician's own self-respect is mirrored by his respect for the patient, his own self-confidence equaled by a readiness to believe that the patient can resolve the problems which upset him. Obviously all this is conveyed more convincingly by manner than it is by pious statement.

The schizophrenic patient's sensitivity to the attitude of the therapeutic personnel is reflected dramatically in Linn's[10] report from Saint Elizabeth's Hospital. When, in this setting, on the basis of their favorable experiences with phrenotropic drugs, the nurses and aides began to feel confident that something useful could be done for their patients, the discharge rate rose significantly. A close study of the data revealed, however, that in this particular instance the discharge rate actually increased slightly more for patients who had not received any drugs whatsoever than it did for those who had been on adequate medication. Linn's findings serve as a vivid reminder that the social and psychologic factors involved in its administration may play an important role in determining a given drug's effects; they also give added weight to the important studies of Lasagna and co-workers[11] on the effect of placebos.

Up to this point, attention has been focused on some of the psychologic aspects of the schizophrenic process. This does not mean that schizophrenia results from psychosocial stress alone. Obviously, in the course of personality growth, certain types of life experience are more apt to lead to the development of resilience, resourcefulness and creativity; on this basis alone there could be widely varying degrees of stability in the face of psychologic stress. On the other hand, hereditary factors could play a major role in the innate capacity to withstand stress, as could variations in the regional anatomy and physiology of the central nervous system.

Regardless of the ultimate source of the instability, the psychologic aspects are most frequently of the nature described and should be considered in every approach to the patient. However, the sensory deprivation experiments of Hebb and Lilly, the discovery of the psychotomimetic action of lysergic acid diethylamide (L. S. D.), and the development of the whole series of phrenotropic drugs have brought us nearer to a general theory of behavior which can take into account both its psychologic and biologic aspects.

Both sensory deprivation and L. S. D. bring about a blurring of the boundary between the self and the outside world, feelings of unreality, and alterations in perception which closely resemble some of the early symptoms of the schizophrenic process. They provide experimental tools for investigating the brain structures and functions which are involved in ex-

periencing these feelings. These are structures and functions which presumably may be activated by stimuli from either external or internal sources; the nature of this activation undoubtedly is influenced by the individual's previous life experience. Kety[12] and Benjamin[13] have critically reviewed the important and rapidly expanding literature in this important field and they have pointed out the implications of these biologic studies for our greater understanding of both normal and abnormal behavior.

Even in the absence of anything like complete understanding of the action and mode of action of the phenothiazines and *Rauwolfia* derivatives, clinical trials have amply demonstrated their powerful effect on behavior.[14] There can be no doubt that, appropriately used, these agents do bring about a marked diminution of the patient's tensions and anxiety, often to such an extent that hospitalization may be either avoided altogether or appreciably shortened in duration. The drugs are not a substitute for psychotherapy, but may, by alleviating extreme tension, render the patient accessible to a thoroughgoing exploration of his life situation and an evaluation of the nature and level of his personality adjustment to it. In some instances supportive psychotherapy may meet the need; in others, more intensive work may be indicated.[15]

There remains now the problem of deciding which drug to prescribe, and the array being offered by the pharmaceutical industry is indeed bewildering. On the whole, the phenothiazines have proved more effective than have the *Rauwolfia* derivatives, while the so-called psychic energizers (many of which are monamine oxidase inhibitors) seem often to increase anxiety in schizophrenic persons and to have a disturbing effect on them even when they are depressed in mood. The general practitioner would probably find it most useful to choose two drugs and to use them exclusively, so that he becomes expert in evaluating their effects. When and if a specific appears on the scene, there will be ample time to switch over to it; meanwhile it would seem the wiser course to relegate extensive clinical trials of the new drugs, which appear almost monthly, to those who have special clinical facilities available to them.

There are three groups of phenothiazines, which are differentiated by their side chains. Among the straight aliphatic 3-carbon-atom group are chlorpromazine, trifluprom azine and promazine. These are characteristically used in relatively large doses (in the case of chlorpromazine and promazine, up to 2000 mg. per day). Common side effects are dizziness, drowsiness, blurred vision, extrapyramidal reactions, occasional jaundice, and agranulocytosis. All of these can be ameliorated by reducing the dosage of the drug or, sometimes, by changing to another drug. Some investigators have reported that the extrapyramidal reactions need not always be a signal for discontinuing drug treatment. They have observed notable improvements in their patients' emotional states following the administration of an antiparkinsonism agent, such as ARTANE®, together with a temporary reduction in the dosage of the phenothiazine.

The second group of phenothiazine derivatives has a piperazine side chain; among this group are prochlorperazine and trifluoperazine. The third group have a piperidine side chain; mepazine is included in this group. These drugs are used in considerably smaller doses than is chlorpromazine, especially the piperazines, of which the dosage may not exceed 100 to 200 mg. They cause a minimum of autonomic side effects and do not seem to bring about jaundice or agranulocytosis. However, their use does result in a much higher percentage of extrapyramidal symptoms. The remarks made regarding the straight aliphatic 3-carbon-atom side chain group apply here.

To summarize and focus the foregoing remarks, the first task is to deal with the schizophrenic panic; the second is to explore the current life situation, and the third is to develop a therapeutic plan. Whenever feasible, it is worth going to considerable effort to have the patient request the consultation, even though the family may need to apply considerable pressure to get him to do so. When this is not possible and he is brought against his will, it still should be made clear that since he is the person most concerned, primary attention

will be given to what he says and does. To this end, it is usually more effective to see the patient alone or in the relative's presence; the relative should not be seen in the patient's absence. Even though the patient may be relatively unresponsive, he should be treated as the one who will take responsibility for carrying out the physician's recommendations.

The patient should be allowed and urged to tell as much of his story as he can without interruption. If the relative does break in, he should be told that he will be asked to fill in details later. Obviously delusional statements should not be directly challenged, but reality may be emphasized by asking for details concerning what was going on in the patient's life at the time the disturbing idea came to mind. Before the end of the interview, however, it is important for the physician to indicate that while this seems to have been a most unusual and disturbing experience, its nature and the possible reasons for it are far from clear; he also should explain that it will be necessary to explore the situation much further before he can understand what is really going on. The patient must not feel that the physician's silence indicates tacit validation of delusional or hallucinative experiences. At the same time, reality conflicts which might have given rise to tension and anxiety should be underlined as having played a possible role in the development of the current situation.

After the patient and the relative have given as complete a picture of the situation as they can—a procedure which almost certainly will take a minimum of one to one and one-half hours—the physician might summarize what he has heard from both as to the nature of the complaint, the setting in which it occurred, and his understanding of the total life situation in which it developed. A thorough physical examination is indicated unless it appears that this will increase the patient's anxiety to a critical degree. Usually, a physical examination is as psychologically helpful as it is physiologically desirable, since it serves as a reminder of the doctor's role as an expert who knows what to do in these matters.

Final recommendations should be made to the patient in the presence of his family. All questions should be answered frankly and honestly. Evasiveness is to be avoided at all costs. The patient should not be given reason to believe that anything is hidden or that anything is going on behind his back. In the case of a major psychosis such as schizophrenia, consultation with a psychiatrist is indicated before definitive treatment is undertaken. If the patient realizes that treatment will be planned in consultation and cooperation with his family doctor, and if he is further impressed by the latter's own matter-of-fact acceptance of the need for and the appropriateness of such a referral, his fear will be somewhat allayed. In some situations it may obviously be desirable for the physician to prescribe a phrenotropic drug even before the psychiatrist sees the patient, but it should be made clear that this is symptomatic treatment to relieve the extreme tension of the moment, and that a final plan will not be worked out until further examinations are completed.

This approach accomplishes the following:

1. The patient has been dealt with as one who is expected to be able to regain control of the situation. This is reassuring when he and those about him have come to feel utterly lost, confused and terrified.

2. The patient has not been told that the physician *knows* exactly what is wrong. He either would not believe this, because he knows that he has not yet been able to put all his feelings into words, or he would find it frightening, since it would seem that the physician had taken unto himself supernatural power.

3. By listening calmly to what has been said, by asking questions about the total situation, and by indicating clearly that there is something to be done, the physician has given indirect support, since he has indicated clearly that he knows what to do next in circumstances which have overwhelmed the patient. This is helpful, whereas a directly reassuring statement would not be.

4. By emphasizing reality in his questions and by carrying out a physical examination, the physician has expanded the patient's field of awareness to include some ordinary and familiar life experiences in what otherwise seems to him a complete nightmare.

5. By the physician's evidencing continued but not possessive interest, the patient feels that he is being neither abandoned nor held against his will, but that there will be a consistent, thoughtful and receptive person on whom he can rely and to whom he can turn as he grows more secure.

The interested reader is referred to Sullivan,[16] Fromm-Reichmann[9] and Hill,[8] who have much to say concerning the interview which would be as useful in the general practice situation as it is in dealing specifically with schizophrenic individuals.

Prognosis

Kraepelin's original formulation and designation of dementia precox indicated his original belief that the course was almost invariably downward and the outlook hopeless. He later changed this view, partly as a result of his own further studies and partly because of the distinguished contributions of Bleuler and others. Bleuler's masterful studies of the psychology of these patients form the basis of our present understanding, as does his use of the phrase "group of schizophrenias," which refers not to an end result but to the nature of the psychologic processes which characterize these conditions.

Even before the introduction of drugs, an enlightened social attitude toward mental illness and marked improvement in hospital treatment had resulted in a discharge rate as high as 70 per cent in many institutions. Today, the outlook is even better; perhaps eight of every 10 schizophrenic patients the general practitioner is apt to see can achieve an extrahospital adjustment. It is important to emphasize once more that this degree of success depends on an understanding of the patients' psychologic and social status as well as on the skillful administration of drugs and other treatments in those situations which call for their use.

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Surgical Treatment of Trigeminal Neuralgia and Discussion of Compression Operation

C. HUNTER SHELDEN, BENJAMIN L. CRUE AND JAMES A. COULTER*

Huntington Memorial Hospital, Pasadena, California

Compression of the posterior root fibers for the relief of trigeminal neuralgia is a simple surgical procedure that can be repeated, if necessary, without technical difficulty. The authors believe it is technically and statistically the surgical procedure of choice in this condition.

In a series of 115 cases, 16 patients required reoperation because of recurrence of pain; in 11 of these 16 cases, recompression was done. Postoperative complications were minimal.

C. HUNTER SHELDEN

TRIGEMINAL neuralgia is a syndrome of unknown cause characterized by recurrent paroxysms of severe pain limited to the distribution of the trigeminal nerve. The pain occurs in momentary jabs lasting a second or two, followed by complete relief. The paroxysms may recur with such rapidity that the patient describes a continuous type of pain. Pain may occur spontaneously but usually is precipitated by talking, chewing, brushing the teeth, touching the lips or nose, washing the face, or simply moving the facial muscles. Paroxysms of pain usually occur daily for weeks or months and then disappear completely for months. There seems to be some seasonal variation, with a tendency for the pain to occur in the spring and fall. It is described as being like a hot electric wire or a dentist's drill hitting the nerve in a tooth or a sharp knife or ice pick jabbing the gums or cheek. It was once stated that if a diagnosis cannot be made from the first four sentences of the

*Department of Neurosurgery, Huntington Memorial Hospital, Pasadena, California.

patient, one should proceed with caution.

Trigeminal neuralgia is predominantly unilateral. It has been stated[1] that approximately 2 per cent of patients have bilateral involvement; however, in our series bilateral pain has occurred in more than 9 per cent. When unilateral, the pain is most frequent in the second or third division of the nerve, or both. The paroxysms are not often localized in the first division. The pain is located near the midline, that is, in the upper or lower lip and along the lateral aspect of the nose.

Treatment is determined for each individual patient on the basis of history and location of the pain. Those having a short history should be given the benefit of a trial of B_{12} or DILANTIN® therapy. Occasionally one or the other affords a prolonged period of relief. Stilbamidine may relieve the pain, but the likelihood of distressing bilateral facial and cervical paresthesias more than offsets the benefits obtained, and it should not be used.

Surgical Treatment

Surgical procedures for the treatment of trigeminal neuralgia vary from alcohol injections of terminal branches to intracranial resection of the posterior root of the nerve. Each procedure has its special indication, and selection should be made with the objective of obtaining maximal relief with a minimum of risk.

Alcohol injection—This procedure should be limited to the infraorbital or supraorbital branches. Deep alcohol injection of an entire second or third division is no longer recommended. The procedure is a painful ordeal for the patient and, if successful, results in a far greater degree of numbness than is associated with the newer operative procedures.

Division of the infraorbital nerve—If the pain is localized to the nose or upper lip and has been completely relieved previously by alcohol injection of this branch, it is better to resect the nerve at the infraorbital foramen than to repeat alcohol injections.

Division of the greater auricular nerve—Trigeminal pain limited to the third division, without pain in the tongue, frequently can be relieved by crushing the greater auricular nerve in the neck. As a diagnostic procedure, 30 patients had the greater auricular nerve injected. Crushing of the nerve gave lasting relief in five patients. This procedure, first reported by Wyburn-Mason,[2] is of greater theoretical than practical value.

Posterior root section—Intracranial section of the posterior root of the trigeminal nerve has been in vogue for many years.[3] It is the only procedure which assures permanent relief of pain. However, it results in permanent and complete facial and corneal anesthesia. In the light of more recent developments, it does not seem justified to sacrifice so much to avoid the possibility of a second surgical procedure. If one considers the frequency with which trigeminal neuralgia is limited to the lower portion of the face, there can be little justification for total division of the posterior root. In our series, pain was limited to the third division in 42 per cent of the patients, and it involved the third division with some pain in the second division in 77 per cent. Thus, a subtotal root section[4] would be indicated in more than three-fourths of the patients, but this conservative procedure carries a significant risk of recurrence. Grant reported in 1938 a recurrence rate of 5.4 per cent after subtotal root section. The recurrence rate reported by Bakay was 13.6 per cent, by Guidetti 8.3 per cent, and by Peet and Schneider 14.1 per cent.[1] Certainly the more limited the subtotal resection, the greater is the chance of return of pain in the area supplied by the preserved fibers.

An added deterrent to root section is the possibility of discovery of the cause of trigeminal neuralgia. No doubt some medical treatment, probably chemical in nature, will evolve in the near future. When it does, the patient whose nerve has been spared will be still amenable to treatment. It is our present policy to avoid posterior root section.

Medullary tractotomy—This term refers to surgical section of the pain fibers of the descending trigeminal root within the medulla, first described by Sjoqvist.[5] This method affords relief of pain, but the risk of serious neurologic sequelae is far too great to advocate its routine use in trigeminal neuralgia.

Decompression of the major branches of the trigeminal nerve—In 1951 we first attempted

to relieve trigeminal neuralgia by means of decompression of the nerve at the foramen ovale and rotundum. The rationale of this method was based on the observation that in most patients the pain involves the second and third divisions, both of which pass through bony foramens, whereas the first division, which is rarely involved alone, passes through the large infraorbital fissure. It was therefore considered that constriction at the foramens could play a significant role in the production of pain. This operation was performed in 10 cases, and consisted of enlarging the bony foramens by means of a high-speed dental drill. Every patient was relieved of pain immediately and had little or no postoperative numbness. The only disturbing feature was the surgical observation that not once did we discover a foramen in which the nerve was constricted.

Decompression of the posterior root—This procedure, introduced by Taarnhøj[6] in 1952, consists of splitting the dura propria over the posterior root. The immediate results are excellent, but the high rate of recurrence of pain has dampened much of the early enthusiasm for the method. Svien and Love[7] reported a recurrence rate of 75.8 per cent following decompression in a series of 91 patients observed over a four year period.

Stender[8] reported a procedure termed "gangliolyse" in 1953 which in effect is a method of decompression accomplished by stripping the dura propria from the gasserian ganglion. His results have been very satisfactory, but it is likely that the beneficial effects are due to the compression of the fibers which occurs during the dissection.

Compression of the Posterior Root Fibers

Our original objection to the decompression procedure was based on the absence of valid evidence that the trigeminal fibers are constricted at any point. It seemed impossible to decompress fibers that were not compressed. Nevertheless, the relief of pain obtained by the so-called decompression procedures either at the level of the foramens or over the posterior root could not be disregarded. Identical clinical results achieved by the same technical procedure at different levels must have some common denominator.

In 1953 we deliberately compressed the posterior root fibers of a patient with trigeminal neuralgia.[9] The surgical approach and exposure were identical to those employed for subtotal root section. The fibers were visualized and locally compressed, using a blunt instrument (figure 1). The patient experienced complete relief of pain with no objective sensory loss.

During the five year period considered in this report, we operated on 115 patients using this method. Only 16, or 13.9 per cent, have required reoperation. However, we consider the recurrence rate to be 20 per cent, because seven additional patients experienced at least one episode of pain after operation.

It is interesting to note that all but one of the patients with recurrence of pain had a "gentle" compression. In fact, during the first three years we purposely used a gentle to moderate compression and may have overstressed the gentleness in some instances. We believe now that a moderately firm degree of pressure on the posterior root fibers, or that degree of compression which we have described as "moderately heavy," will effect the most satisfactory long-term results.

Eleven of the 16 patients who required reoperation had a second compression operation. Four of the 16, because of limited distribution of the pain or other factors, had either a peripheral branch resection or a subtotal rhizotomy. Among the 11 patients (9.56 per cent of the total group) in whom the nerve was recompressed, nine had recurrence of pain in the previously involved division or divisions and two had recurrence in areas not previously affected.

Reoperation was done twice in two cases. In one of these (patient H. W. F.), the original compression was done in 1953 for pain limited to the third division fibers. After five months, pain returned, this time in the second division. At the second operation a subtotal type of compression was done of the fibers of the lower two-thirds of the posterior root. The patient was pain-free for 23 months, when

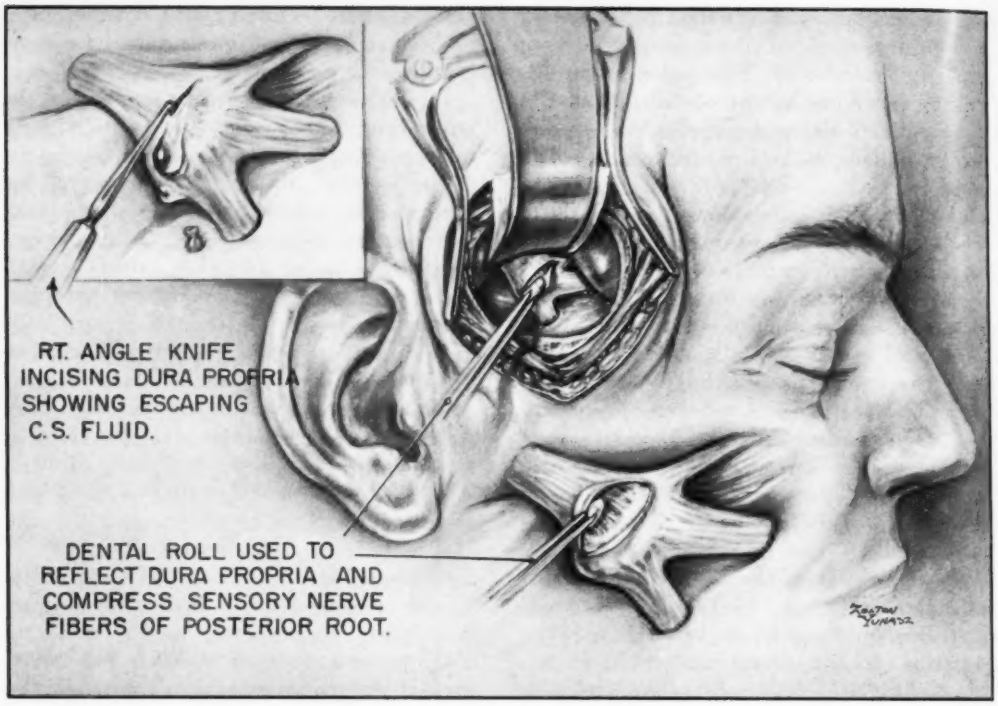

FIGURE 1. Method of compression of posterior root fibers.

pain again developed, this time limited to the first division. Reoperation was done, and heavy compression was employed over the entire posterior root. To date the patient has remained free of pain since this procedure. Several other patients in the group in which pain recurred had compression of only a limited portion of the posterior root. These experiences have convinced us that compression of the entire root at the time of the original operation affords a result superior to that obtained by any selective compression.

In the other case in which two reoperations were performed (patient P. K. D.), the second compression was "moderately heavy" in degree and considered adequate, but pain returned after only 18 months. At the time of the third operation the degree of compression was described as "heavy." More pressure on the posterior root fibers was used than in any other case in the series. The patient had been warned that heavy pressure might result in marked anesthesia, but postoperatively there was only minimal objective sensory loss.

Our experience taught us that severe compression will result in almost complete anesthesia. However, the sensory loss that follows lesser degrees of compression is extremely variable.

The fundamental technic has remained constant, but some variations have been employed with regard to the site and degree of compression. In four patients the posterior root was compressed in the posterior fossa. The results were equally as satisfactory as were those obtained via the temporal approach. The degree of compression has varied from gentle (55 patients) to very heavy (four patients).

In general the postoperative sensory loss is proportional to the degree of compression; however, in a few instances moderately heavy pressure did not result in appreciable objective loss. Eighty patients had little or no demonstrable sensory loss, 27 had postoperative

los classified as minimal, six patients had a moderate sensory change, and in two patients sensory loss was marked. It was interesting that one patient described complete subjective facial anesthesia without dysesthesia, but careful examination failed to reveal objective loss of tactile or pain sensation.

It is our impression that the most satisfactory results are obtained in those patients who have demonstrable, though minimal, postoperative sensory change. This would suggest that there is an optimal degree of compression. It is our hope that we can develop an instrument which will allow one to apply a calibrated degree of pressure, thereby eliminating the one variable feature in the present technic.

In our attempts to standardize the amount of pressure applied, we have utilized several different technics. We have used a blunt hook, a flat spatula, and a cut portion of a firm dental roll. We believe the latter, held by a bayonet and kept dry by gentle suction, affords the best means of applying the pressure; apparently one can compress the posterior root fibers to a sufficient degree but at the same time have a wide enough margin of error to prevent local destruction of fibers, as occurs occasionally in using a hard object such as a blunt hook.

Postoperative complications are minimal, though similar in nature to those following other operative procedures for the relief of trigeminal neuralgia. Herpes occurred in 60 patients (52 per cent), and the lesions appeared similar to those seen after rhizotomy. They did not seem to be correlated with the degree of compression of the posterior root fibers. Sixty-eight per cent of the patients in whom herpes developed had had minimal compression, whereas only 32 per cent had had moderately heavy pressure applied to the root fibers.

Postoperative dysesthesias seldom occur following the compression procedure. Only seven patients complained of any subjective discomfort, and none described the severe burning, crawling sensations that occur frequently after rhizotomy. Three patients described a hypersensitivity of the tongue, especially near the tip, and another three experienced occasional transient sensations in the tongue that they could not describe accurately. One patient did state that he experienced an occasional facial sensation that one might interpret as a very mild dysesthesia. In two cases we were concerned because of bilateral dysesthesias involving the cervical area as well as the face. These developed after dismissal from the hospital, and in both instances we learned that stilbamidine had been given several weeks prior to operation.

There was one death, that of a 74 year old woman in whom a massive intracerebral hematoma developed on the fourth postoperative day. Reoperation was done and the hematoma was evacuated, but she died 10 days later. At the time of autopsy it could not be determined whether the lesion was directly related to the operative procedure or represented a primary cerebral vascular accident. A small extradural hematoma developed in one other case, but the patient recovered completely following re-exploration.

Some degree of transient facial weakness was noted in 13 patients, but on only three occasions was the facial palsy of real clinical significance. It is interesting that in nearly every instance the weakness did not become apparent until the third or fourth postoperative day.

How does compression of the posterior root fibers relieve the pain of trigeminal neuralgia? We do not know, but there is some physiologic evidence that seems to be significant. King and Meagher[10] and, later, Crue and Sutin[11] demonstrated that during stimulation experiments in monkeys two types of waves appear in the trigeminal system following electric excitation of the infraorbital nerve. An afferent spike occurs first, followed by a delayed centrifugal wave. A portion of the paper by Crue and Sutin can best describe the results they obtained, and with their permission we quote it here.

> The trigeminal nerve responses were the same as those described by King and Meagher. On stimulating the infra-orbital nerve, both an initial afferent spike and a later wave could be seen. The afferent spike reached the recording electrode on the maxillary nerve intracranially

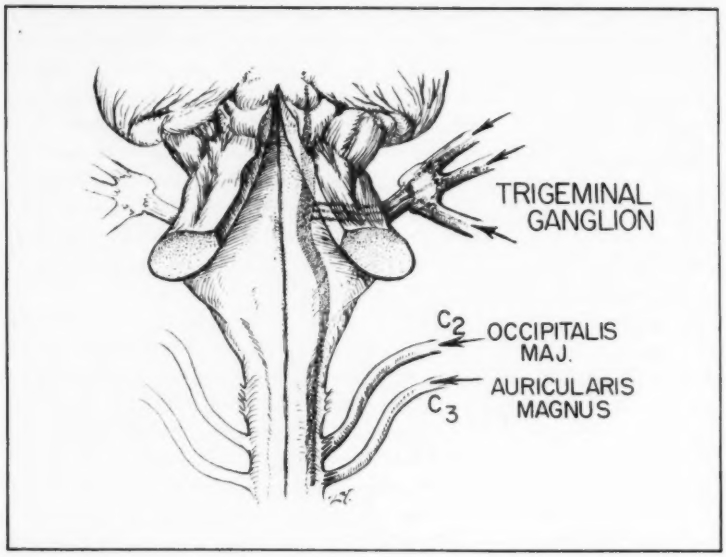

FIGURE 2. Schematic drawing of central relation of trigeminal and cervical nerve fibers.

at the foramen rotundum in approximately 0.4 millisecond and the posterior root at about 0.6 millisecond. The delayed response appeared at about 2 milliseconds and had a threshold higher than that required to evoke the afferent spike, but an amplitude less than that of the initiating afferent volley. The delayed potential was found in all three peripheral divisions of the trigeminal nerve, as well as in the ganglion, posterior root, and medulla following infra-orbital stimulation. No electrical activity was detected in the contralateral trigeminal nerve. It was also verified that stimulation of any of the three peripheral branches of the trigeminal nerve, the ganglion itself, or of the posterior root produced the delayed wave. The threshold for the late wave was very low on several occasions, being obtained with a stimulus of about 0.25 volt. This seemed to depend on the individual preparation. It was verified that even minor trauma, such as stripping the dura overlying the ganglion, prevented the demonstration of the delayed wave. Pressure on the posterior ganglion or root with a cotton pledget, in a manner similar to that done in a Shelden compression procedure, abolished the delayed potential at the foramen rotundum. The initial afferent volley, however, was still transmitted to the posterior root and medulla, and appeared grossly unchanged. However, if the stimulating voltage was increased, the delayed wave was still obtained central to the point of compression, but not distally. Thus, there appeared to be a two-way change of conduction at the site of compression. The initiating afferent spike must have been changed in some manner as it no longer produced the late wave at the same voltage. But with the voltage increased, the delayed wave seemed unable to pass the point of compression "centrifugally."

This failure of the delayed centrifugal wave to pass distal to the point of compression of the trigeminal fibers in monkeys may apply also to humans and help to explain the surgical results obtained by the compression operation. Certainly the compression procedure does not selectively damage, to any significant degree, the pain fibers in the posterior root, as demonstrated clinically by the minimal objective loss of pain sensation. It must be assumed that local trauma to the fibers has, in some way, interfered with electric conduction within the nerve or has reduced such activity to a subexplosive level.

In other parts of the experiments by Crue and Sutin, it was observed that with stimulation of the infraorbital nerve, delayed waves also appeared in the greater auricular nerve. These observations lend support to the physiologic relationship of the trigeminal and great-

er auricular pathways. This is not surprising if one considers that, anatomically, the pain fibers from the entire head and neck enter the central nervous system at or about the second cervical level. The descending pain fibers of the trigeminal system extend downward to the approximate point of entrance of the occipital, greater auricular, and upper cervical fibers (figure 2).

The compression procedure affords excellent clinical results. Relief of pain has been uniform, residual numbness has been minimal, and the recurrence rate has been low. It is a simple surgical procedure that can be repeated, if necessary, without technical difficulty. However, we must point out that although our present recurrence rate is low, a period of observation of six years is much too short to draw any firm conclusions. It is possible that many more patients will have a return of pain. In this regard, it should be mentioned that in Peet and Schneider's[12] large series of patients a 14.1 per cent recurrence rate of pain was observed after subtotal rhizotomy. Even more significant is the 5.4 per cent recurrence rate of pain in the denervated area following total rhizotomy.

In this series of 115 patients, all of whom were operated on prior to December 1958, 23 (20 per cent) noted some degree of recurrence of pain. In seven of these cases (6.08 per cent) the pain was either so infrequent or so minimal in degree that injections or operative procedures were unnecessary. Sixteen patients (13.9 per cent) have required some type of additional operative procedure. A subtotal rhizotomy was done in two patients, the maxillary nerve was resected intracranially in one, and one had division of the infraorbital nerve at the infraorbital foramen. Eleven patients had recompression of the posterior root; one had a local injection of the infraorbital nerve.

The compression operation, we believe, is technically and statistically the procedure of choice in the treatment of trigeminal neuralgia. More significant is the fact that the patients are happier postoperatively than are those who have had any type of rhizotomy.

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Three Essentials in Therapy of Parkinson's Disease

LEWIS J. DOSHAY AND LOUIS BOSHES

Columbia-Presbyterian Medical Center, New York, and Northwestern University Medical School, Chicago

Thirty years of experience with patients who have Parkinson's disease have developed better understanding of ways in which the family physician can best serve such a patient, not only to maintain his present well-being but to prevent the contractures, deformities and disabilities of later years. Emphasis is on proper orientation and the implementation of a program including medication, physical therapy, and exercises and activities.

There is no short cut to good and lasting results, and it is hoped that no doctor will hereafter feel that he has fulfilled all his obligations to a patient with Parkinson's disease by merely prescribing a tablet.

PARKINSON'S disease is named after James Parkinson, who in 1817 described it in a paper entitled "An essay on the shaking palsy."[1] It is a chronic and slowly progressive disease of the extrapyramidal motor system of the brain with characteristics of rigidity, tremor at rest, variable degrees of akinesia, and a diminution or final loss of spontaneous and automatic movement.[2] The intellectual level usually is unimpaired, regardless of the progression of the disease, and sensation is uninvolved. Superimposed on all the symptomatology there can be a marked emotional overlay, with numerous patterns resulting.

During the past decade, the impetus directed toward more efficient management of Parkinson's disease has resulted in a good deal of progress in the creation of new and better remedies. Also in recent years, neurosurgical procedures have been devised which afford considerable reduction of rigidity and tremor in selective cases in which there is no longer a response to conservative measures. The greatest drawback to surgical therapy at present is the lack of lasting results. Symptoms tend to return within a year or more, and further operative procedures are required which often leave the patient in a much worse condition than before surgical treatment was commenced. Further research is in process to correct this problem.

Regardless of the surgical and nonsurgical methods used at present, no patient to date has been cured of Parkinson's disease. It is roughly estimated that more than a million persons in this country have the disease. Their

LEWIS J. DOSHAY

LOUIS BOSHES

number is growing and is likely to continue to grow, in line with the increasing life expectancy in the general population.

The etiology and measures of prevention of the disease remain unknown. However, within the past two years two foundations have come into existence, namely, the National Parkinson Foundation and the Parkinson's Disease Foundation, whose aims are to promote and support research into the cause and prevention of the disease, the discovery of improvements in medical and surgical treatment, the establishment of training centers for physiotherapists and other personnel required in rehabilitative work, and the creation of special nursing and convalescent homes, farms and other facilities for the care of persons with advanced disease and disability. The arrival of these and other aids in the management of problem cases will ease the greatest present challenge to the physician in regard to Parkinson's disease, since the care and treatment of early and ambulatory cases pose but little difficulty.

Considering that the vast majority of patients with Parkinson's disease are the responsibility of the general practitioner, it is understandable why he has to keep abreast of the latest advances in treatment. He sees the patient earliest, when the greatest good can be achieved toward the prevention of later disabilities. He has to orient the patient properly and plan a broad and intensive program of treatment right from the start. So managed, Parkinson's disease becomes one of the easiest ailments to treat, since the patient does not expect a cure and appreciates any improvement in his condition, and because there is no problem of diagnosis in this illness; a mere glance at the patient usually suffices.

Orientation of the Patient

There is much that the physician can tell his patient to reassure him and remove fears and misunderstandings about the illness. This can serve to cement a lasting and beneficial relationship with the doctor. He can inform the patient that his basic symptoms are tremor and rigidity, which can be controlled successfully by means of the *three essentials of therapy*, medication, physiotherapy and exercise. He can also tell him that there is never paralysis in this illness, nor is there loss of speech, or pain unless treatment is neglected. The reasons should be made clear to the patient by means of a diagram such as the one in figure 1. He should be advised that Parkinson's disease is not inherited and not contagious and that vision and hearing are never affected. The physician also can tell the patient that there are stationary periods of five or more years when there is little or no progression in the symptoms, that new and better drugs are being discovered almost daily, and that there are far worse ailments than Parkinson's disease—for example, leukemia, brain tumor, multiple sclerosis. He may also inform him that for unknown reasons Parkinson's disease tends to protect the individual against cancer, cardiac disorders, hypertension, tuberculosis and other illnesses.

The physician should make it crystal clear to the patient that he must remain under medical supervision continuously. Appointments may be spaced a month or more apart, in order to permit regular checks on the symptoms and medication and to give attention to side effects and personal and other problems that often arise in the course of a long illness. Each visit should be utilized to provide emotional support and reassurance to the patient and his family.

The physician must be encouraging in his attitude and should reflect genuine interest in the patient's ailment and welfare. Without this, the patient can lose confidence, discontinue his medication and physical therapy, and go on to total disability. With interested care, he

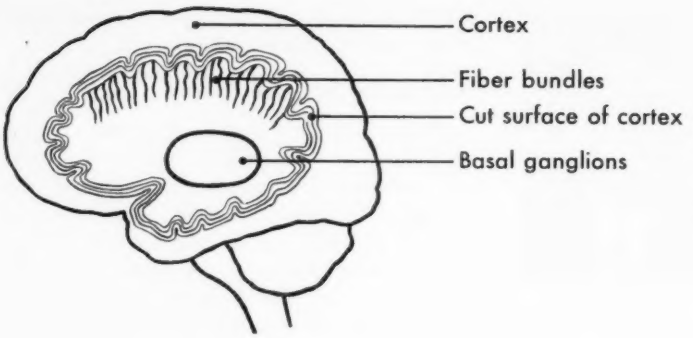

FIGURE 1. Site of Parkinson's disease in basal ganglions. The cortex and its pathways are unaffected, and hence there can be no paralysis, loss of speech or impairment of intellect.

can be assured many years of a productive and comfortable life, and the doctor can be assured of a delightful patient with whom to work. Far more can be accomplished in Parkinson's disease through conscientious effort than most patients and some doctors realize. It is well to remember that there is no paralysis as there is in multiple sclerosis, nor primary atrophy as in poliomyelitis, and that the sad instances of contracture, deformity and disability of later years are most often the result of neglect of proper treatment.

The Three Essentials of Treatment

Since there is no cure for Parkinson's disease, we must treat the symptoms and the patient. We have already alluded to treatment of the patient under the heading of orientation. Treatment of the symptoms requires a flexible program of medication, physical therapy and exercise (figure 2). These measures should be utilized in every case of Parkinson's disease, except in the occasional instance of a patient with tremor and no rigidity in which medication alone suffices or surgical treatment is employed. Clinical observation, however, proves that more than 90 per cent of these patients have some degree of rigidity, and the worst complications and disabilities of later years stem from this source.

Some doctors believe they have fulfilled all the obligations to a patient with Parkinson's disease when they have prescribed hyoscine tablets. Other physicians employ the latest and best drugs available for this illness but pay no attention to physiotherapy and exercise. Physiotherapy is as important as or even more important than medication for patients with drooping of the head and kyphosis of the upper back brought on by flexion contracture of the neck and spine. Similarly, for patients with difficulties of speech and writing, special exercises can be more important than medication. Clinical experience of 30 years has proved that neither medication alone nor physiotherapy alone nor exercises alone will serve the ultimate best interests of the patient. All three must be employed in unison. The doctor's judgment will determine which of the three requires greatest emphasis in a particular case.

Drugs

Significant strides have been made in the medicinal management of Parkinson's disease in the past decade. Prior to World War I the armamentarium consisted of stramonium, belladonna and hyoscine. By the end of World War II several other solanaceous products had come to the fore, including 0.5 per cent atropine, RABELLON®, VINOBEL® and BELLA-BULGARA®. During the past 10 years a large number of new synthetic compounds have appeared on the market, and the busy practitioner finds it difficult to keep up with them. They have advantages of greater specificity of action and less disturbing side reactions. The other considerations are that some drugs lose their beneficial effects with the passing of time, that several drugs have to be employed simultaneously to control the many symptoms of the disease, and that some patients tire of any remedy during the long course of the illness.

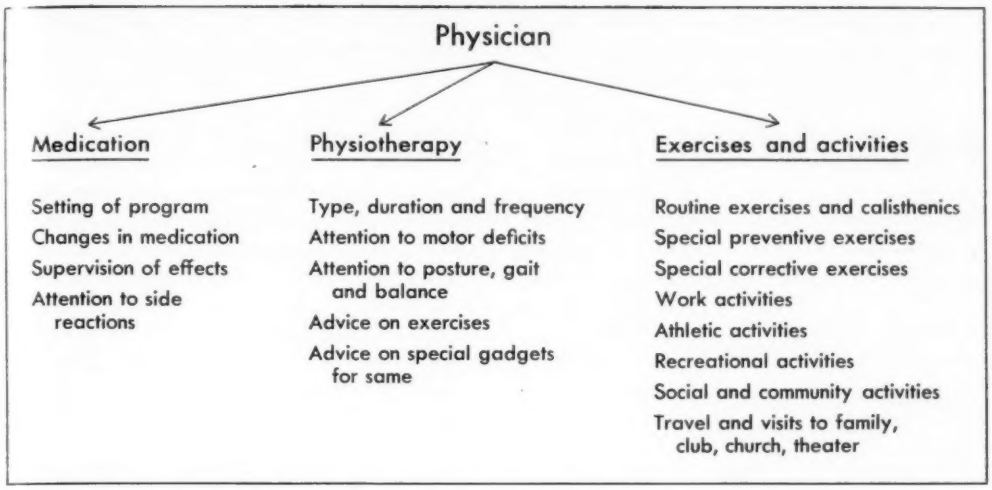

FIGURE 2. Threefold approach to effective therapy of Parkinson's disease.

Thus, many good drugs must be available, and the search continues for still more and better compounds to meet the ever-changing needs, tastes and tolerance of the patients.

Treatment has to be tailored to the individual requirements of each patient, because there is so much variability as to symptoms, personality make-up and tolerance of drugs. Tolerance is itself influenced by the patient's age, constitutional make-up, weight, and the type of Parkinson's disease. Patients of the post-encephalitic type have far greater tolerance than those of idiopathic and arteriosclerotic types. Older patients are as a rule more sensitive to drugs which produce changes in blood pressure, drowsiness or dizziness, but there are exceptions. Obese patients generally tolerate drugs better than do lean patients.

The standard antiparkinsonian agents in common use for the control of rigidity, tremor, akinesia, fatigue, lethargy, muscular cramps, sialorrhea, oculogyria, insomnia, and so on, are listed in table 1. Also presented in the table are original source references to which those unacquainted with a particular drug may turn for details of administration, actions and side effects. In addition to these agents, many of the newer medications for the treatment of other ailments are of *occasional* use for the control of one or another symptom of Parkinson's disease. Attention to these ancillary drugs is omitted to conserve space.

Physical Therapy

Physiotherapy is extremely important for the control of rigidity and the prevention of later contractures that lead to postural abnormalities, deformities, gait disturbances, falls and injuries, and ultimate invalidism. However, in order for the patient to realize maximal protection, physiotherapy must be employed continuously through the years. Some patients become discouraged by lack of results after one or several treatments and discontinue them. It is therefore imperative that they be prepared to understand that just as the rigidity is likely to stay with them for the rest of their years, so physiotherapy will be needed for as long as they live.

In Parkinson's disease, physical therapy should be confined to modalities that provide health to the muscles rather than momentary comfort to the patient. It should consist of *massage* to soften the muscles and *passive stretching* to loosen and free the muscles and joints (manipulation). The physiotherapist's precious time must not be wasted on the use of baking lamps, vibrators, whirlpool baths or "bubble" baths; these the patient and his family can employ at their own leisure.

TABLE 1

Drugs in Common Use for Parkinson's Disease

DRUG*	GENERIC NAME	AVAILABILITY (MILLIGRAMS)	DAILY DOSAGE RANGE (MILLIGRAMS)		INDICATIONS	SIDE REACTIONS
			Age 30-50 yr.	*Age 50-70 yr.*		
ARTANE®[3]	Trihexyphenidyl	2, 5	10-25	6-10	Rigidity, tremor, akinesia, oculogyria, depression, inertia	Dry mouth, blurred vision; overdosage produces mental confusion, delirium, agitation, hallucinations
PAGITANE®[4]	Cycrimine hydrochloride	1.25, 2.5	5-15	2.5-7.5	Same as Artane	Fewer reactions than with large doses of Artane
KEMADRIN®[5]	Procyclidine hydrochloride	5	15-30	7.5-15	Same as Artane	Same as Pagitane
COGENTIN®[6]	Benztropine methanesulfonate	2	4-8	2-4	Muscle spasm, cramps, severe rigidity, contractures, frozen states	Dryness of mouth, occasional skin reaction
DISIPAL®[7]	Orphenadrine hydrochloride	50	150-300	50-150	Muscular spasms, rigidity, fatigue, weakness, sluggishness, depression, sialorrhea, diaphoresis, blepharospasm	Slight dryness of mouth, occasional confusion
PHENOXENE®[8]	Chlorphenoxamine	50	100-300	50-150	Same as Disipal, but longer lasting	Same as Disipal
PARSIDOL®[9]	Ethopropazine hydrochloride	50, 100	100-900	50-600	Good for tremor control, if tolerated. Good muscle relaxant, good for insomnia	Drowsiness, dizziness
BENADRYL®[10]	Diphenhydramine hydrochloride	25, 50	100-300	75-200	Tension, excitement, tremor, insomnia, if tolerated	Dizziness, drowsiness
Hyoscine[11]	Levorotatory scopolamine	0.3, 0.6, 0.45	1.8-3	1.2-2.4	Good for insomnia, tremor control, if tolerated; some action in rigidity and oculogyria	Severe dryness of mouth, blurring of vision, dizziness, drowsiness
DEXEDRINE®[12]	*d*-Amphetamine sulfate	5, 10, 15	10-30	5-20	Lethargy	Excitation, restlessness, increase in tremor, heart flutter

*All drugs listed, except hyoscine, are synthetic.

Massage should always be of the vigorous and deep type, unless contraindicated for some specific reason. Even patients who appear sluggish and decrepit usually can tolerate very vigorous treatment and benefit from it. When involvement is unilateral, treatment should be concentrated on the affected arm and leg. When involvement is bilateral, the neck and spinal muscles must receive attention, in addition to the limbs. Treatments should last an hour and should be given once, twice or three times a week, depending on the patient's needs. A practical program that achieves results and sells physiotherapy to the patient and family is to commence treatment on a three-times-a-week basis for the first month or two, after which therapy could be maintained successfully on a once-a-week basis.

The physiotherapist is well trained in his art, but he is not a doctor and is not likely to perform the required job unless directed to do so. The doctor must specify the type, duration and frequency of treatment as well as the parts and motor deficits needing special attention. If a patient has difficulty in putting on his coat, the physiotherapist can correct this, if ordered to do so. Similarly, he can correct difficulties in getting in and out of bed, disturbances in gait, lost finger skills, and so on, but only if the patient reaches him before the muscle contractures become irreversible.[13] A patient with a fixed kyphosis of the upper spine will not allow the therapist to straighten his back because of the severe pain involved. Yet, some doctors fail to order physiotherapy until the patient shows advanced signs of disability or the family becomes alarmed by the progression of symptoms. This should not be. Early treatment and prevention of later complications prove less costly in the long run and are of far greater benefit to the patient than are neglect and last-minute desperate efforts at correction after the damage is done and the contractures can no longer be reversed. The physiotherapist can serve the doctor and patient in many helpful ways:

1. To maintain the well-being of the patient.
2. To provide him with greater freedom of movement, for work and exercise.
3. To prevent the deformities and complications which may occur in later years.
4. To remove contractures, where possible, and arrest disturbances in gait, posture and balance.
5. To correct motor deficits in patients who experience difficulties in getting out of a chair and in dressing and eating.
6. To keep the doctor informed as to the progress or failure of the treatment program, since he sees the patient far more often than does the doctor.
7. To set, advise and drill the patient on special exercises to prevent or correct contractures and motor deficits, as well as the acquisition of suitable apparatus for these exercises.

Failure to obtain physiotherapy is often not the fault of the doctor, the patient or the family but is due to conditions beyond their control. In some parts of our country a patient has to travel 50 mi. to reach a physiotherapist, so that by the time he returns home most or all the benefits of treatment are lost. Where facilities are available, the cost is often beyond the means of the patient and family. Some hospitals and clinics are forced by the shortage of personnel to limit their physiotherapy services to acute problems such as polio or back injuries, necessarily excluding Parkinson's disease. There is nevertheless hope that with the reawakening of the government to the growing needs of the aging population and with the facilities to be created by the newly established Parkinson foundations, the current handicaps to better treatment will be corrected.

Exercises and Activities

Every physical act the patient performs provides health to the muscles, and hence he should be encouraged to do as much as he can for himself. His family should assist him only with tasks or fragments of tasks of which he is totally incapable or which, if he were forced to perform them, would cause him to become severely strained and tremulous. However, even tasks that are difficult, such as buttoning a shirt or putting on a coat, can become much easier after they are practiced a hundred times a day. The practiced effort softens, loosens and stretches the muscles so that movement

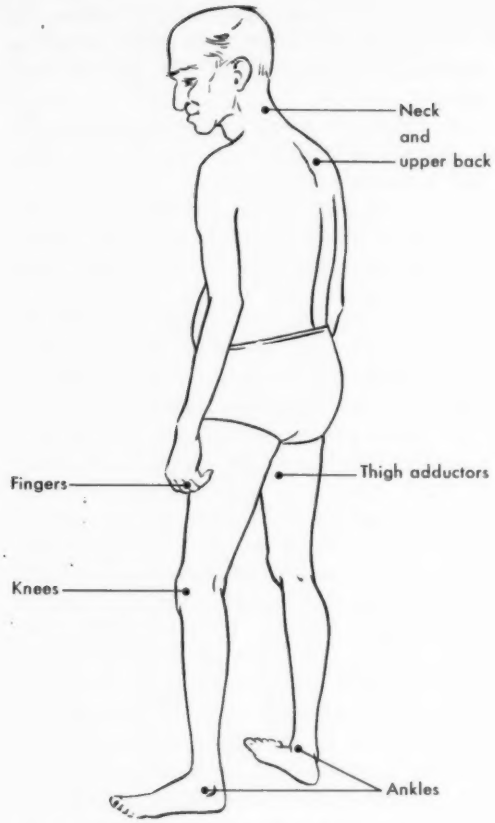

FIGURE 3. Vulnerable areas of the body.

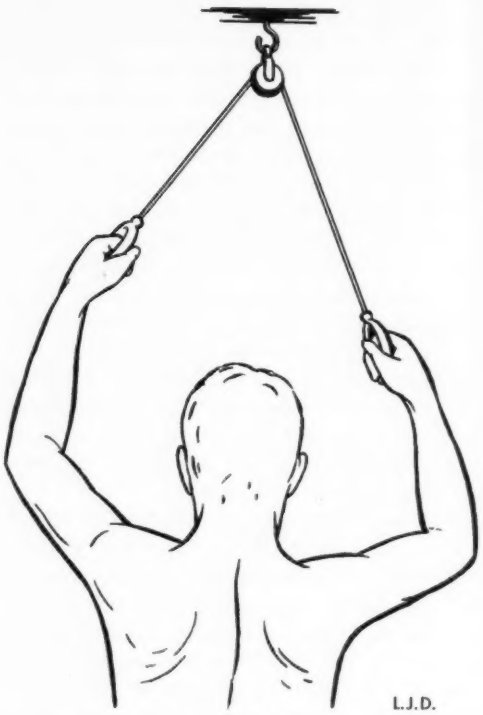

FIGURE 4. Exercise with overhead pulley.

becomes freer as each act is repeated.

Conversely, inactivity and failure to use rigid parts that offer resistance can lead to disuse atrophy of the muscle bundles. They become replaced by fatty connective tissue and later by fibrous connective tissue or scars. The progressive scarring cannot fail to bring about ever greater resistance to the use of the muscle, which in turn leads to further disuse atrophy and scarring. A vicious cycle develops which often terminates in deformities and total immobility of the patient. This must not be permitted to happen, and it can be prevented if the doctor and family encourage the patient to use *all* his muscles, even those that are rigid and resistant to movement. Drugs loosen the muscles to some extent, and the physiotherapist contributes his share to keep them free and mobile, but *the patient must not neglect his share* in the threefold attack on the problem of rigid muscles.

If getting out of a chair is difficult, a special chair with the front legs shortened an inch or two should be set aside for the patient to make getting in and out easier. If getting out of bed is difficult and hazardous, a bed frame with a trapeze could be installed to help the patient rise to a sitting position, from which it is easier and safer to move off the bed. If buttoning of clothes becomes impossible because of contractures in the small muscles of the fingers, snaps and zippers should replace buttons wherever possible. If use of a safety razor presents problems, a change should be made to an electric razor. If work becomes difficult, the hours should be shortened and pressures lessened, but the patient should be encouraged to continue as long as possible

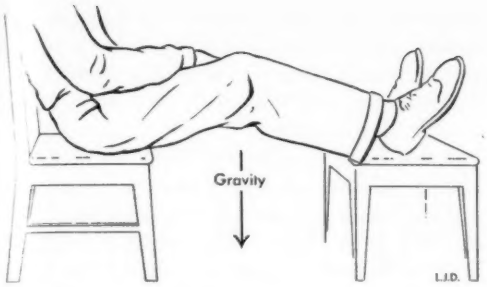

FIGURE 5. Knee suspension exercise.

FIGURE 6. Goose-step exercise.

rather than to retire. This is especially so for those who have no hobbies or leisure plans, hence would merely sit, brood and deteriorate from inactivity.

In addition to the foregoing, the patient should be encouraged to engage in a broad program of extra activities including social, community, recreational and athletic pursuits best suited to his individual physical resources, background experiences and interests. Sports, swimming, boating, fishing, visits to the family, church, club or theater, conversations with neighbors, or even playing bingo or cards can contribute to the maintenance of healthy muscles. In addition, they afford emotional values from pleasureful relationships with others. Sometimes travel or a vacation trip to the mountains or seashore, or a sojourn at a spa, or a period of intensive rehabilitation in a hospital can prove highly beneficial to a patient with advanced Parkinson's disease. The doctor should keep these possibilities in mind and decide which and when they may be utilized to the greatest advantage of a certain patient.

Besides the day-to-day activities to keep the muscles movable, there are special exercises to prevent later contractures or to correct existing motor deficits. The physiotherapist can help the doctor in planning and setting up the exercises, if ordered to do so.

Early cases require only such *preventive* exercises as will insure a free range of motion at all joints and vulnerable areas of the body. A patient who does manual labor or a housewife who does many of the chores of the home may not require routine preventive exercises. The vulnerable areas include the neck and upper spine, the knees, thigh adductors, ankles and fingers (figure 3). The flexor muscles of the neck are stronger than the extensors, and if neglected they flex sharply and draw the head downward. In the process they also draw down the upper spine, producing a kyphosis and a tendency toward propulsion. To prevent this, the patient should exercise 10 or 15 minutes twice a day with an overhead pulley (figure 4). This contraption is simple and inexpensive to erect and involves merely a hook, a pulley and a strong piece of cord. A rowing machine also can prove beneficial.

The hamstring or flexor muscles of the knee are stronger than the extensors, and with neglect they become shortened and maintain the knees in a bent position which draws the body downward and forward. A simple exercise such as shown in figure 5, if performed half an hour once or twice a day, can help to prevent this. The thigh adductors, when shortened, draw the legs sharply together, producing a dangerously narrow base for proper balance and walking. The situation can be remedied by the practice of walking with the legs widely separated.

The calf muscles or flexors of the ankle are stronger than the extensors. When they short-

en, the tendo achillis pulls the ankle upward, producing an equinus posture with toe walking, propulsion and hazardous falls. To prevent this, the patient should practice daily goose-stepping exercises such as demonstrated in figure 6.

The hand is the most highly skilled motor organ of the body. To prevent contractures and deformities of the fingers, daily exercises should include hyperextension and manipulation of the fingers as well as squeezing on a roll of foam rubber, typing, etc.

Patients in whom, through neglect or progression of the disease, disorders of speech, writing, posture, gait or balance develop can in most instances achieve improvement through the practice of *corrective* exercises. The physiotherapist can help in many situations, and we shall describe several of the exercises.

Speech cannot actually be lost in Parkinson's disease, because only the basal ganglions, not the brain proper, are affected (figure 1). The most common speech problem encountered is a nasal, muffled monotone brought about by the freezing of the face and lip muscles. This can be corrected by impressing on the patient the importance of forcefully using his lips when he talks. The doctor could demonstrate to himself and the patient how difficult it is to speak clearly if the upper lip does not move. Reading aloud to the family from a newspaper 15 minutes each night is a good drill for strengthening the lip muscles and achieving better articulation.

Writing difficulties are produced by rigidity of the wrist, to which the lack of free mobility of the fingers contributes. The most common problem is that the letters are cramped, small and illegible. Only a blackboard, a scratch pad and time are needed to correct the situation. The patient should set aside half an hour two or three times a week for 15 minute wrist drills on the blackboard and 15 minute writing periods on the scratch pad. The blackboard affords the space for the practice of large circles, clockwise and counterclockwise, large and small lines, numbers, letters and words. They can be erased and the process repeated many times until a free flowing motion is achieved at the wrist. This is followed by the practice period of writing words, large and small, on the scratch pad. Time is not a problem with most patients, and if they invest it in writing exercises they will have no further trouble on this score.

If the body lists to the right, the patient should practice carrying a shopping bag containing stones with the left arm, in order to tilt the body to that side. With continued drills an eventual balance in posture is achieved, sometimes within a fortnight.

In conclusion, may we again emphasize that in Parkinson's disease a program of intensive therapy encompassing the *three essentials* of medication, physiotherapy and exercise can serve to maintain the patient in a good functioning state for many years, and, in most instances, can prevent the contractures, deformities and disabilities of later years.

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Metabolic Encephalopathy in Hepatic, Renal and Pulmonary Disorders

GILBERT H. GLASER*

Yale University School of Medicine, New Haven, Connecticut

Metabolic encephalopathies resulting from disorders of the liver, kidneys and lungs are manifested clinically as acute and chronic disturbances of intellectual performance and motor and sensory activities ranging from mild confusional states to coma. The electroencephalographic pattern correlates well with the intensity of the clinical disturbance.

Clinical features, differential diagnosis, and treatment of neurologic disturbances associated with hepatic, renal and pulmonary disorders are presented.

GILBERT H. GLASER

THE functions and structural integrity of the brain may be profoundly disturbed when there is disease of certain visceral organs, particularly those concerned with body metabolism. The basic requirements for energy production and utilization by the brain are substrates (mainly carbohydrate), oxygen, and enzymes and coenzymes to catalyze the degradation of substrates.[1] The maintenance of activity of the central nervous system also depends on metabolic pathways concerned with proteins and lipids which often become intertwined with carbohydrate, as in the relationship between amino acids and the tricarboxylic acid cycle, and the substituted glycoproteins, lipoproteins and nucleoproteins. Many of the substances are involved eventually in the mediation of axonal and synaptic transmission.

Metabolic encephalopathy, therefore, may be the result of insufficiency of substrate, oxygen, or both, interference with (1) cerebral enzyme activity, (2) transport of metabolites such as amino acids and electrolytes into nerve cells, and (3) oxidative phosphorylations, or by effects on stimulated neuronal respiratory processes.[2] Disorders of the liver, kidneys and lungs produce disturbances in cerebral func-

*Associate Professor of Neurology and Chief, Section of Neurology, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

tion by these mechanisms. In all, there may be important contributing deviations in general water, electrolyte (especially sodium and potassium) and acid-base balances.

These encephalopathies are manifested clinically as acute and chronic disturbances of intellectual performance, including memory and orientation, behavior, perceptions and motor and sensory activities. The intensity may vary from a mild confusional state or disturbed awareness to stupor and eventually coma. The electroencephalogram has been found often to be a sensitive indicator of the encephalopathy, correlating well with the intensity of the clinical disturbance.[3,4]

Hepatic or Portal-systemic Encephalopathy

A significant neurologic disorder may be the result either of a failure of liver function or of a gross disturbance of the portal and hepatic circulation.[5-7] This may be due to acute hepatitis or hepatic necrosis, chronic hepatitis, cirrhosis (Laennec's, hemochromatosis, posthepatitic, biliary), and portacaval anastomoses. The disturbance has been termed "hepatic coma," but, since coma is an end stage, the total developing picture would be better termed encephalopathy, since both acute and chronic forms of organic cerebral dysfunction occur.

Clinical features—Basically the condition is characterized by a disorder of consciousness and a generalized motor disturbance. The disorder of consciousness appears first as mental confusion with either decreased or increased psychomotor activity, followed by stupor and coma. The motor disturbance is manifested as a peculiar intermittent, irregular flapping movement (asterixis[8]) during sustained muscular contraction, as when the arms and legs are held outstretched, a fluctuating rigidity of the limbs, grimacing, sucking and grasp reflexes, exaggeration of the deep tendon reflexes, extensor plantar reflexes and, at times, convulsions. This disturbance may develop over a period of hours or days in patients with severe hepatic disease, but various features of the entire picture may exist for many months in some cases.

The signs and symptoms of the encephalopathy vary with the nature of the underlying disorder of the liver, mainly in mode of onset and development of the clinical picture. In acute hepatic failure such as that which is secondary to acute hepatic necrosis due to a viral infection or toxin, the encephalopathy usually is coincident with or preceded by deterioration in the general clinical condition, with intense nausea, vomiting and fetor hepaticus. Drowsiness, headaches and nightmares may develop and lead into symptoms of excitement, mania and an acute delirium with disorientation and visual hallucinations. The deep reflexes are increased, and ankle clonus may be present as well as Babinski's sign. The flapping tremor becomes prominent. Eventually, severe clouding of consciousness rapidly progresses into coma. This is associated with generalized flaccidity, and with rising temperature and pulse rate prior to death.

In the more chronic disorders such as hepatic cirrhosis, an acute confusional state may occur with flapping tremor, as an initial episode. In other patients with chronic disease of the liver the neurologic disturbance develops as a chronic organic mental disorder punctuated by exacerbations of delirium, stupor and possibly coma. These exacerbations may occur as a result of intercurrent infection, surgical trauma, high-protein diet, ingestion of ammonium salts or urea, and hemorrhage into the gastrointestinal tract. This is particularly true in patients with a large portal-systemic collateral venous circulation. Also, in some patients with hepatic disease, a variety of chemical substances such as acetazolamide, chlorothiazide, methionine and amphenone may induce hepatic coma. Abnormalities of serum electrolytes and administration of opiate narcotics, barbiturate sedatives and certain phenothiazine tranquilizing drugs may contribute to an impending hepatic coma. The neurologic syndrome consists of personality change and intellectual deterioration varying from mild to severe confusion with daily fluctuations. Focal defects may occur such as constructional apraxia and aphasias. Sleep disturbances, either drowsiness or insomnia, are frequent. Visual symptoms have included di-

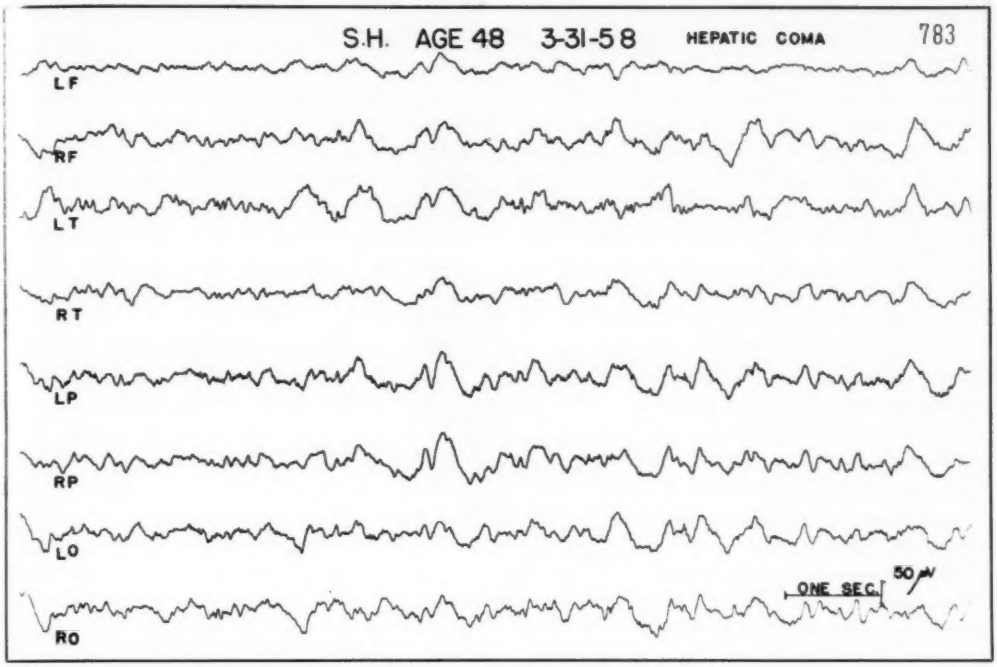

FIGURE 1. Electroencephalographic changes in hepatic coma. Diffuse nonspecific 2 to 3 cps slow waves, some with suggestive triphasic form. Blood ammonia, 164 mg.

plopia, loss of acuity, and perceptual anomalies such as micropsia and complicated hallucinations. Amnesia has been prominent for the episodes of stupor and coma, and eventually marked impairment of memory develops. Focal, generalized or myoclonic seizures occur in severe cases.

The electroencephalogram[3,9,10] in the milder or developing neurologic disturbance contains disorganized alpha rhythm and increasingly large amounts of diffuse, random 4 to 7 cps theta activity. When coma develops, the electroencephalogram consists of bilaterally synchronous and asynchronous slow delta waves in the 2 to 3 cps range occurring more or less continuously or on a background of relatively normal frequencies (figure 1). In many instances the slow wave formations characteristically appear as bilaterally synchronous triphasic waves. Although these changes in the electroencephalogram are commonly seen in hepatic coma, they are essentially nonspecific, occurring in other severe metabolic disturbances which produce coma as well as in other diffuse, degenerative or inflammatory diseases of the brain.

The neuropathologic changes resulting from severe liver disease are characteristically those of diffuse enlargement and proliferation of protoplasmic astrocytes diffusely in the cerebral cortex, basal ganglions, amygdaloid nucleus, thalamus, brain stem, and cerebellar cortex and nuclei.[5] The neurons in the deeper cortical layers show nonspecific alterations. Focal areas of demyelinization in the white matter of the cerebral cortex have been reported in the literature.[11]

Pathogenesis (figure 2)—The early experimental work in dogs with an Eck fistula (portacaval anastomosis) showed that neurologic disturbances could develop as a result of protein or meat intoxication. This work led to the concept of portal-systemic encephalopathy due to ammonia toxicity.[7,12] The onset of hepatic coma in most instances is associated with a disturbance of nitrogen metabolism,

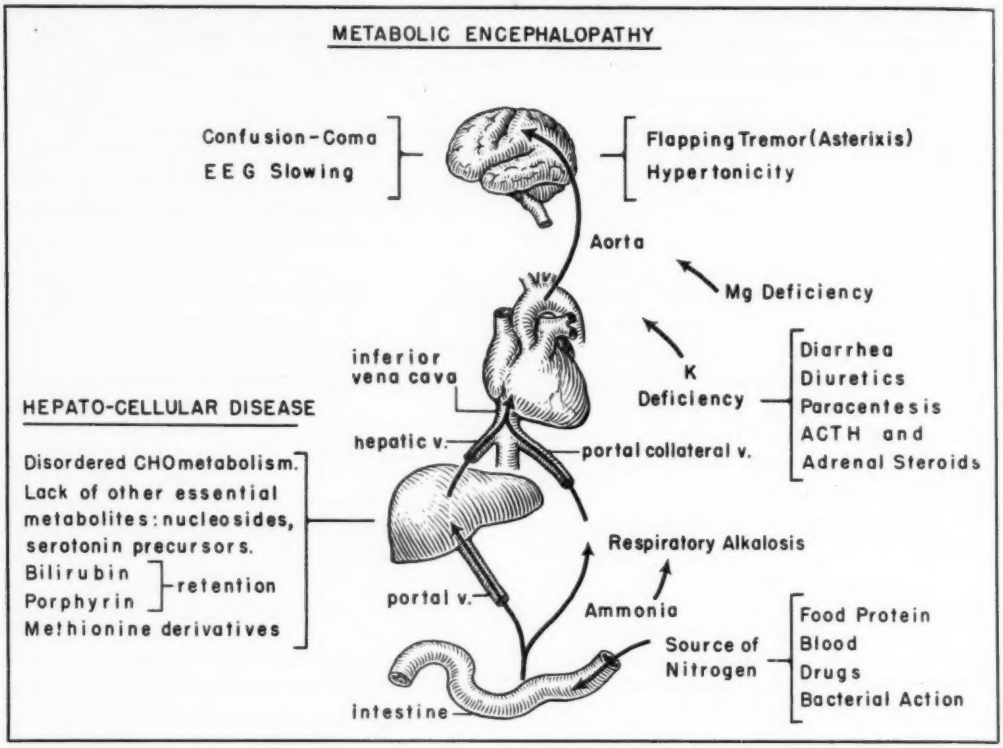

FIGURE 2. Mechanisms of portal-systemic encephalopathy and hepatic coma. Factors altering cerebral metabolism in hepatic disease.

(Modified from Sherlock.)

causing an increase in the concentration of blood ammonia. It is proposed that this develops primarily from intestinal contents not metabolized by the liver. In patients with diffuse hepatocellular degeneration the shunt is through the liver itself. In more chronic disorders the large venous collaterals take care of the shunting. Coma has been precipitated or worsened in patients by the administration of high-protein diet, urea or ammonium chloride. The electroencephalographic abnormalities have been shown to be sensitive to an increasing blood ammonia level. Ammonia has been regarded as an intoxicant interfering with cerebral metabolism either at the level of glutamine synthesis or in the reductive amination of alpha-ketoglutarate. However, other factors may be involved. Blood ammonia levels do not rise when neurologic changes are precipitated by methionine, and in some patients with severe hepatic coma, particularly secondary to chronic cirrhosis, the levels are not elevated. In other patients, high levels of ammonia in the blood may occur without severe neurologic disturbance. These other factors[7] may be changes in the carbohydrate metabolism, respiratory alkalosis, hypokalemia, magnesium deficiency, abnormal sulfur metabolism, and retention of bilirubin and porphyrins. Certain nucleosides, cytidine and uridine, synthesized by the liver, are necessary for the proper metabolism and survival of perfused brain.[13] These may be deficient in hepatic failure.

Treatment—The general principles of treatment of the comatose patient should be applied, as well as those methods designed to correct the various biochemical disturbances

the specific hepatic disorder.[7,12] These basic principles include maintenance of fluid and electrolyte balance, adequate oxygenation, proper caloric intake, and prevention of infection. Electrolyte disturbance may be severe, especially hyponatremia and hypokalemia. Ammonium chloride and acetazolamide should not be employed. Since in many instances the major metabolic disturbance may be related to the effect of toxic nitrogenous substances formed in the intestine by bacterial action on protein, this should be handled directly. It is recommended that dietary protein be discontinued, and that up to 1600 calories per day be supplied as glucose orally or in 20 per cent solution intravenously. During recovery, protein may be added in 20 gm. increments. Antibiotics such as neomycin are administered to diminish bacterial flora in the intestines. Glutamic acid, sodium glutamate and arginine have been of help in some instances. Hemodialysis is being attempted.[14] Adrenocorticoid therapy has not been effective in hepatic coma complicating cirrhosis but may be useful in acute hepatitis. It has been recommended that vitamin K be administered to lessen the risk of hemorrhage. Long-term treatment is based mainly on protein restriction.

Renal Failure and Uremia

Any severe disease of the kidneys, acute or chronic, resulting in renal failure may cause uremic encephalopathy. In uremia there is an accumulation of toxic substances in the body fluids, end products of metabolism secondary mainly to decreased excretion and partly to accelerated metabolism, predominantly of proteins and their derivatives. The mechanism of the uremic syndrome remains obscure. The responsible factor is not just accumulation of urea. Possibilities include circulating derivatives of protein such as urea, creatinine, uric acid; retention of inorganic and organic acids, including sulfate; and retention of proteolytic enzymes. Patients with azotemia and severe symptoms of uremia have high serum elevations of creatinine, urea, undetermined anions and organic acids. Contributing disturbances are hypocalcemia, dehydration, acidosis and hypokalemia.

Clinical features—The early symptoms of uremia are those of depression of function of the central nervous system such as apathy, fatigue, drowsiness, inability to concentrate, and dull, constant headaches. There are often cyclic variations with brief periods of good performance and a feeling of well-being. However, as the disorder progresses, anorexia develops, speech becomes slow and slurred, memory deficits appear, and the patient complains of generalized muscular weakness. The mental dysfunction may then proceed from a mild confusional state through all phases of delirium to stupor and finally coma. However, some patients retain a relatively clear sensorium until death. With increasing uremia, signs of neuromuscular and cerebral hyperexcitability occur, such as increased reflexes, myoclonic muscular twitchings, and focal and generalized seizures. The convulsive disorder in uremia may develop along with stupor and coma. Although seizures usually are present terminally, they may continue after recovery from a uremic episode, indicating persistent cortical irritation due to actual brain damage with epileptogenic foci. The electroencephalogram may show diffuse slow theta and delta wave activity (figure 3).

Many other neurologic disturbances occur, but less commonly, such as monoplegia, hemiplegia, aphasia, apraxia, signs of meningeal irritation, nystagmus, vertigo, transient or persistent amaurosis, and a flaccid, ascending paralysis (Landry type), especially of the lower extremities. The breathing pattern may be abnormally altered into Kussmaul and eventually Cheyne-Stokes varieties. Other mental aberrations appear aside from acute and chronic confusional states, such as hallucinosis with features of a toxic psychosis, and psychotic reactions resembling catatonic, paranoid and depressive states, usually determined by the previous personality of the patient.

Severe and occasionally irreversible changes may develop in the cerebral tissues. Acute uremia may produce acute damage of cortical neurons and astrocytes. More chronic states cause focal and perivascular areas of necrosis with glial nodule formation and demyelinization in the cerebral hemispheres.

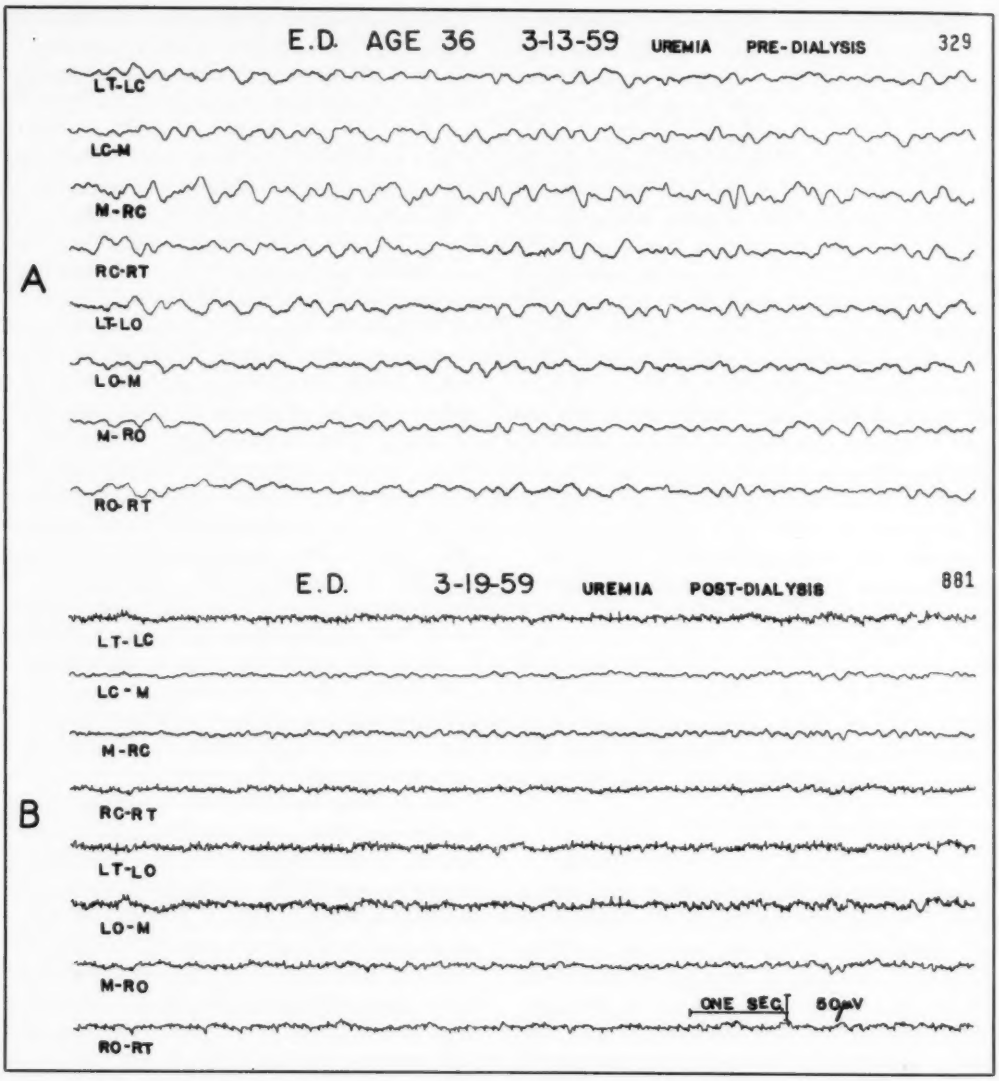

FIGURE 3. Electroencephalographic changes in uremia due to chronic glomerulonephritis.

A. Before dialysis. Blood nonprotein nitrogen, 350 mg. Electroencephalogram contains diffuse 2 to 4 cps activity. Patient stuporous.

B. After dialysis. Blood nonprotein nitrogen, 224 mg. Electroencephalogram improved, showing 6 to 7 cps, 8 to 9 cps and fast waves. Patient more alert.

Treatment—Treatment is based on the medical and surgical management of the underlying renal disease. Reversible causes of renal impairment include congestive heart failure, dehydration, infection, obstruction, salt depletion, alkalosis, loss of potassium, and hypercalcemia.[15] Certain self-limited instances of renal insufficiency may occur in acute glomerulonephritis and lower nephron nephrosis. However, the uremic patient with severe neu-

rologic involvement usually represents a terminal status. The manifestations of dysfunction of the central nervous system (including the seizures) may be treated symptomatically by rectally or intramuscularly administered paraldehyde or intramuscularly administered magnesium sulfate. Barbiturates may be helpful but should be those which are metabolized mainly by the liver (secobarbital, amobarbital) rather than those excreted by the kidney (phenobarbital). The phenothiazine tranquilizing drugs may be used in controlling nausea and vomiting, but these drugs lower the convulsive threshold and should be used with care in patients with seizures. Diphenylhydantoin is excreted by the kidney only to a minor extent, and may be administered rectally or intravenously in relatively low to average dosages in attempts to control uremic seizures. Recently, external hemodialysis[16] has produced some reversal of mental and neurologic abnormalities in some instances (figure 3).

Encephalopathy Associated With Chronic Pulmonary Insufficiency

In a significant number of patients with long-standing chronic pulmonary disease such as chronic bronchitis and emphysema, producing progressive right-sided heart failure and eventual acute and chronic cardiopulmonary insufficiency, severe neurologic signs and symptoms may develop which then dominate the clinical picture.[17,18] The differential diagnosis may become one of distinguishing between a brain tumor and an extrapyramidal disorder. Rapid recognition of the presence of a severe chronic pulmonary disturbance may prevent the search for other lesions involving the central nervous system requiring diagnostic procedures such as arteriography, air encephalography and ventriculography. In some patients the chronic cardiopulmonary insufficiency is related to extreme obesity, the so-called Pickwickian syndrome.[19]

Clinical features—The cardinal clinical features of this condition are those of cardiac and pulmonary failure, headache, papilledema, mental and behavioral changes with impairment of consciousness, and tremor and twitching of the extremities.[8,17] Most of these patients have a basic pulmonary disorder such as chronic bronchitis, emphysema or asthma, and some have a severe kyphoscoliosis with impaired pulmonary ventilation. Severe obesity may be a primary or contributing factor. Both left-sided and right-sided forms of congestive heart failure are present with edema, hepatomegaly, increased venous pressure, pulmonary congestion, cyanosis and severe dyspnea. The headaches often are severe and generalized but may be frontal or occipital in localization. The patients complain of an intense steady aching which appears usually at night or in the early morning, often awaking them from sleep. Occasionally, vomiting occurs in association with severe headache. Many patients have bilateral papilledema which is occasionally asymmetric. The intensity may vary from slight blurring to several diopters of elevation with venous congestion and peripapillary hemorrhages. Visual acuity is normal and the visual fields are full. The cerebrospinal fluid pressure is almost always elevated, varying from 215 to 500 mm. of water pressure. These cases therefore represent a variety of "pseudotumor cerebri." The cerebrospinal fluid protein usually is normal.

In most instances, a mental or behavioral disturbance develops, usually associated with impairment of consciousness. The patient may be drowsy, forgetful, irritable, confused and inattentive. Disorientation to time, place and person occurs along with severe memory deficit and slowing of coherent mental processes. Eventually a state of stupor may progress into a severe coma. Usually there are no specific aphasias, apraxias or motor or sensory deficits. Characteristically, many patients have tremulous extremities with twitching usually seen in the outstretched hands and fingers. These twitching movements are coarse, often flapping, and are similar to those seen in hepatic coma and other severe disturbances of cerebral metabolism (asterixis[8]).

The electroencephalogram (figure 4) often contains diffuse synchronous and asynchronous slow waves in the theta (4 to 7 cps) and delta (½ to 3 cps) frequency ranges, occasionally in episodes or bursts. These electro-

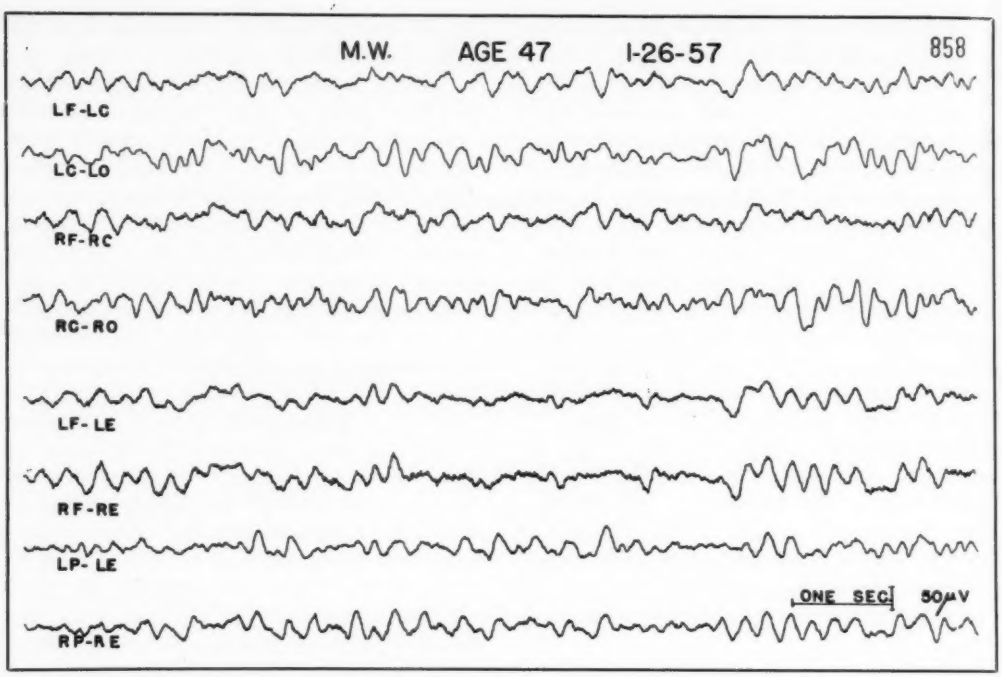

FIGURE 4. Electroencephalographic record of patient with encephalopathy associated with pulmonary emphysema. Diffuse asynchronous 3 cps and 4 to 5 cps slow waves.

encephalographic abnormalities are reversible with relief of the pulmonary insufficiency.

The pathophysiology of the cerebral manifestations of chronic pulmonary insufficiency is related to a number of factors: hypoxia, hypercapnia with carbon dioxide narcosis, and the development of cardiac failure with pulmonary congestion and increased venous pressure. All of these may contribute toward the production of cerebral edema and vascular congestion. In only a few cases does it appear that polycythemia is a factor, and then particularly in the increased intracranial pressure and papilledema. Carbon dioxide retention is of major importance. The increased concentration of carbon dioxide causes cerebral vasodilatation and probably secondarily increased cerebrospinal fluid pressure and papilledema. The severe headache probably is secondary primarily to the cerebral vascular dilatation.

In many of these patients the responsiveness of the respiratory center to carbon dioxide is depressed, and the respiratory stimulus becomes hypoxia acting on the aortic and carotid body chemoreceptors. Administration of oxygen then may produce a worsening of the neurologic manifestations by removing the hypoxic stimulus and causing an already impaired ventilatory apparatus to be more impaired. The mechanism of the tremor or asterixis is still not determined. It appears in a nonspecific fashion in a variety of states characterized by general impairment of cerebral metabolism, such as chronic pulmonary insufficiency, uremia, hepatic failure, severe gastrointestinal malabsorption syndromes, drug intoxications, and hypoglycemia. A focal cerebral lesion does not appear to be involved in such cases.

Differential diagnosis should include, in addition to brain tumor, other metabolic disturbances producing secondary encephalopathy, the various extrapyramidal disorders, and other diffuse cerebral disorders such as viral and inclusion encephalitides.

Treatment—The basic treatment of the dis-

der is directed toward the improvement of pulmonary ventilation and the elimination of carbon dioxide. The features of cardiac and pulmonary decompensation may be relieved in part by the administration of digitalis and diuretics and restriction of sodium. In some instances, severe polycythemia may be treated by venesection. The pulmonary dysfunction should be treated by bronchodilators and attempts to increase ventilation by positive pressure technics. Both the arterial oxygen saturation and the carbon dioxide tension should be followed carefully. As already mentioned, administration of oxygen may increase the arterial oxygen saturation but may aggravate carbon dioxide retention. Positive pressure hyperventilation may diminish the carbon dioxide tension, but at times it may not actually increase the oxygen saturation. In probably most clinical instances of this disorder, mechanical artificial respiration with a tank respirator or a Jefferson ventilator may be necessary. Using this means, carbon dioxide may be eliminated more effectively because of better control of alveolar ventilation. The carbon dioxide sensitivity of the respiratory center then will increase due to the resulting diminution of carbon dioxide tension. Under these controlled circumstances the administration of oxygen may be more effective and without the danger of its depressant effect on respiration. As the patient's metabolic disturbance is improved, these controls of the respiratory mechanism may be withdrawn gradually.

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Psychopharmaceuticals: Uses and Abuses

NATHAN S. KLINE*

Rockland State Hospital, Orangeburg, New York

In cases of mental disturbances, as in other fields of medicine, referral to a specialist should be made if there is a serious question of diagnosis or the need for emergency treatment or if there is no response to therapy within an appropriate period. The psychiatrist should be utilized exactly as should a medical specialist in any other field.

A classification of pharmaceuticals influencing psychologic states is presented, together with alternate terminology, a listing of specific drugs in the various groups and their dosages, remarks on the advantages and disadvantages of the use of combinations of psychopharmaceuticals, and an outline of side effects and their management.

NATHAN S. KLINE

NOWHERE in the field of medicine is treatment applied with poorer understanding of indications, less adequate knowledge of the requirements of dosage regulation, and fewer clear criteria for continuance or discontinuance of treatment than in the widespread use of psychopharmaceuticals. The responsibility for this has been attributed to numerous causes, such as to a plethora of articles found in the media of mass communication, or to pharmaceutical houses, but ultimately and justifiably to the medical profession itself. Although the professional science writer is the soul of restraint, there have been all too frequent "prescribe it yourself" articles and even books by unaccredited sensationalists. Drug companies failed initially in their promotional literature to distinguish between mild sedative preparations and major pharmaceuticals of great potency (and relatively high toxicity). Weakly acting preparations were made to sound as though they could move mountains, and the inevitable side effects of the stronger preparations were so minimized that they came as a shock to many practitioners.

*Director, Research Facility, Rockland State Hospital, Orangeburg; Assistant Clinical Professor of Psychiatry, Columbia University College of Physicians and Surgeons, New York, New York.

Medical practitioners in fields other than psychiatry have been hampered at times by lack of diagnostic skill, inexperience in handling patients with psychiatric disorders, and traditional distrust of the psychiatrist. There existed good historical reasons to justify all three factors, but the altered situation calls for some radical changes.

Although there exist disputations within the psychiatric field as to a proper application of the psychopharmaceuticals and the question has been raised whether the drugs "cure" or repress symptoms, these problems should not interfere with the proper use of the drugs by other medical practitioners. Obviously the same precautions should be observed as apply in any other medical area; namely, if there is no response within an appropriate period or if there is serious question of diagnosis or the need for emergency treatment, the patient should be referred to a specialist.

The traditional psychotherapeutic technics of the average medical practitioner—reassurance, airing of problems, interest and concern as well as common-sense advice—are as important as ever. Amateur psychodynamic analysis is just as dangerous as amateur surgical intervention. Since the advent of psychopharmaceuticals there is less excuse than ever for such malpractice. This is particularly true in cases of formerly psychotic patients who are in remission (either on maintenance therapy with drugs or no longer receiving drugs); many authorities feel that even the most expert "depth analysis" should be assiduously avoided in these cases. The average practitioner is quite capable of handling the vast majority of ex-institutionalized patients by regulation of medication, reassurance, manipulation of the environment where necessary, and the other technics already mentioned.

It also appears evident that in a high percentage of cases even initial admission to a mental hospital can be avoided if patients are adequately treated with appropriate drugs. In many parts of the country there simply are not enough skilled psychiatrists available, and the burden of this responsibility falls on other practitioners. The dosage ranges needed in the treatment of such patients differ markedly from those necessary in management of the ordinary neurotic patient, and although care should always be exercised it is important to stress that as a rule massive doses for fairly prolonged periods are essential for successful treatment.

Clinical Classification of Pharmaceuticals Influencing Psychologic States

Even the full-time worker in the field becomes confused at times by the plethora of names and descriptive terms used to describe pharmaceuticals influencing psychologic states. The classifications of the drugs proposed by various authorities during the past four years are actually in quite close agreement. Difficulty arises either from the use of a variety of terms to describe a single principle of drug action or from the use of identical names to indicate quite different groups of pharmaceuticals. The classification which follows, and which is summarized in table 1, includes the common alternate terms and indicates those which appear to me to be most suitable and the reasons for such a choice.

The entire group of drugs—The most concise term designating all drugs which affect psychologic function is "psychopharmaceuticals." "Tranquilizers" obviously is an unsuitable term, since the group includes stimulants. The alternate term "psychochemicals" should be reserved for the even broader category of chemical substances, whether exogenous or endogenous, that are involved in psychologic functioning; psychopharmaceuticals are limited to substances of exogenous origin. As to the frequently used term "phrenotropic," this, literally translated, means influencing the mind, and is perfectly acceptable.

There are three major categories of psychopharmaceuticals: (1) psychohibitors, which restrict, limit, restrain or depress either normal or abnormal psychologic functioning; (2) psychoactivators, which act to increase, elevate, arouse or stimulate either normal or abnormal psychologic functioning; (3) psychotomimetics, which cause psychologic states that are abnormal.

1. Psychohibitors—This term, meaning to

TABLE 1

CLINICAL CLASSIFICATION OF PHARMACEUTICALS INFLUENCING PSYCHOLOGIC STATES

Psychopharmaceuticals (phrenotropics)
1. Psychohibitors (psycholeptics)
   a. Hypnotics
   b. Sedatives
   c. Muscle relaxants
   d. Ataraxics (neuroleptics)
   e. Undetermined
2. Psychoactivators (psychoanaleptics)
   a. Psychomotor stimulants
   b. Psychostimulants
   c. Psychic energizers
3. Psychotomimetics (psychodysleptics)
   a. Hallucinogens
   b. Cataleptogenics
   c. Euphoriants
   d. Chronoleptogenics
   e. Depressants
   f. Disinhibitors
   g. Confusants

restrict or restrain psychologic activity, is selected because it describes the outstanding characteristic of the entire group and is itself a neutral word. The term "tranquilizers," originally used to designate a particular subcategory, is sometimes assumed to refer to all the psychohibitors. Another alternate, "depressants," has a specific physiologic meaning which implies a particular mode of action. It is also too closely associated with "depression" as used in reference to the emotional condition.

Subcategories—a. Hypnotics—Drugs which induce sleep (whatever other action they have).

b. Sedatives—Compounds which reduce excitement, agitation and overactivity, be it physical or psychologic. The ideal sedative would be one which, regardless of the magnitude of the dose, would not produce hypnosis.

c. Muscle relaxants—Pharmaceuticals which have as their primary action the relaxation of muscular tension. They apparently thereby break the feedback chain of anxiety tension. The effects are not dissimilar to those of hydrotherapy; they may be said to constitute "a Turkish bath in a tablet."

d. Ataraxics (noun, ataraxic; adjective, ataractic)—This term, introduced by Fabing, means freedom from turmoil and confusion. A great deal of stress has been laid on the capacity of these drugs to reduce, restrain and restrict hypermotility and emotional excitement. If the drugs did only this, there would be no reason to classify them as other than supersedatives. The one really unique property they possess is their capacity to remove, reverse, restrict or inhibit psychopathology, including hallucinations and delusions, a property not possessed by the sedatives or the hypnotics. Therefore, a new term was needed to designate this action, but since the *modus operandi* was unknown it seemed sensible to avoid any implication as to whether it was biochemical, neurologic or something else.

e. Undetermined—Pharmaceuticals with which sufficient experience has not yet been accumulated to make a clear assignment of category. Rather than to force them into a procrustean bed, they are tentatively placed here until evidence is available indicating the category to which they belong or the need for the creation of new subcategories.

2. *Psychoactivators*—a. Psychomotor stimulants—Compounds which stimulate both psychologic and motor reactions. They tend to speed up mental activity but also introduce distractibility and hyperresponsivity to external stimuli. As a rule they will elevate the mood, often to the point of euphoria (a feeling of more than normal elation). Blood pressure and heart rate are usually increased, although appetite is lessened.

b. Psychostimulants—Compounds which are capable of producing the same generalized psychologic stimulation, both mental and emotional, as the psychomotor stimulants, but with reduced or absent motor side effects, which in large part limit the dosages of psychomotor stimulants. If the psychomotor stimulants could be given in sufficiently high doses, the effect might be the same as that of psychostimulants; in any case, the absence of the motor effects would place the latter drugs in a different subcategory.

c. Psychic energizers—Compounds which tend to "fill the pump" rather than "speed it up." In the treatment of depressed patients the mood is raised to a normal base line, producing a feeling of well-being (eudaemonia), rather than going above the base line (eu-

phoria). In contrast to the stimulants, psychic energizers usually tend to lower blood pressure slightly and increase rather than decrease the appetite. Although both the stimulants and the psychic energizers will reduce the need for sleep, prolonged use of the stimulants tends to produce hyperirritability, whereas some patients taking the psychic energizers can go on for a year or more sleeping only three or four hours per night. Instead of distractibility, an increased capacity to concentrate is noted with use of the psychic energizers.

3. *Psychotomimetics*—Professor Delay's category, "psychodysleptics," is satisfactory also. The term "hallucinogen" might be applicable to a specific subcategory but is too limited for the major grouping, as these compounds may produce other types of psychotic manifestations in addition to the hallucinations. Although no effort is made to be fully inclusive, some of the possible subcategories are as follows.

a. Hallucinogens—Producers of hallucinations (auditory, visual, sensory, etc.).

b. Cataleptogenics—Producers of rigid or unresponsive conditions in which the subject does not respond to stimuli although he is fully conscious and in no sense comatose.

c. Euphoriants—Agents which elevate mood to an abnormal degree.

d. Chronoleptogenics—Drugs which distort the sense of time.

e. Depressants—Agents which lead to an abnormally "low" mood or emotional status.

f. Disinhibitors—Compounds which remove the normal and customary inhibitions in respect to speech, fantasy, feeling or action.

g. Confusants—Preparations which induce a state of perplexity or confusion.

Table 2 lists specific drugs for the various categories and subcategories, with dosages.

Combinations of Psychopharmaceuticals

There are both advantages and disadvantages in the simultaneous use of several psychopharmaceutical agents. Factors which should govern the decision as to which drug or drugs should be used are (1) the condition of the patient, (2) his response to psychopharmaceuticals given previously, (3) the experience of the administering physician, (4) the closeness with which the patient can be observed and supervised, and (5) the experience of others as reported in the literature or recounted personally.

Pharmacotherapy in the psychiatric field is oriented toward "target" symptoms, which can be readily observed or ascertained, rather than being directed at etiologic factors, which are unknown, uncertain or unresponsive. A combination of two drugs with different actions would be indicated if treatment with a single agent provided only partial relief and it was felt that further improvement could be obtained. It should be emphasized, however, that "cure" is not always obtainable, and that reduction of disability, as elsewhere in medicine, is a legitimate goal of treatment. If the patient is restored to a state of being reasonably happy and socially functional, further changes in medication should be made only if there is considerable certainty that they will lead to significantly greater improvement.

The nature of psychiatric reactions is such that it is often impossible to distinguish a primary from a secondary reaction, and alleviation of one symptom may lead to clearing of a number of others. In most circumstances, therefore, I would suggest that the most disabling target be selected and the medication which the physician believes most likely to modify or relieve the condition be given. If no change is seen after a period when it could have been anticipated (which varies from one drug to another), the drug should be withdrawn and another substituted. If partial improvement occurs but then "plateaus" with insufficient remission, the addition of a second preparation aimed at the residual symptoms should be made.

When ataraxics are used in combination, the dose of each is usually less than half the dose which is given when the preparation is used alone, and consequently those side effects related to dosage at times can be eliminated. At other times, side effects of one drug may counteract those of the other and provide another advantage. The opposite, of course, may also be true, and some combinations may produce more side effects of greater intensity.

TABLE 2

Classification of Specific Psychopharmaceuticals*

1. Psychohibitors (psycholeptics)
   a. Hypnotics (only recently introduced preparations are listed)
      Meprobamate (MILTOWN®, EQUANIL®), 400 to 1200 mg.
      Chlorpromazine (THORAZINE®), 50 to 100 mg.
      Glutethimide (DORIDEN®), 0.5 to 1 gm.
      Methylparafynol (DORMISON®), 500 to 1000 mg.
      Methyprylon (NOLUDAR®), 200 to 500 mg.
      Ethinamate (VALMID®), 0.5 to 1 gm.
      Ethchlorvynol (PLACIDYL®), 0.5 to 1 gm.
      Ectylurea (NOSTYN®), 300 to 600 mg.
   b. Sedatives (all dosages are p.r.n., t.i.d. unless otherwise stipulated)
      Acepromazine (NOTENSIL®), 25 to 50 mg.
      Chlorpromazine (Thorazine), 10 to 50 mg.
      Deserpidine (HARMONYL®), 0.1 to 1 mg.
      Ectylurea (Nostyn), 150 to 300 mg.
      Ethchlorvynol (Placidyl), 100 to 200 mg.
      Fluphenazine (PERMITIL®, PROLIXIN®), 2 to 4 mg.
      Glutethimide (Doriden), 0.25 to 0.5 gm.
      Hydroxyzine (ATARAX®), 25 to 100 mg.
      Mepazine (PACATAL®), 25 to 50 mg
      Methoxypromazine (TENTONE®), 20 to 30 mg.
      Methyprylon (Noludar), 50 to 100 mg.
      Oxanamide (QUIACTIN®), 150 to 300 mg.
      Perphenazine (TRILAFON®), 2 to 4 mg.
      Prochlorperazine (COMPAZINE®), 5 to 15 mg.
      Promazine (SPARINE®), 10 to 50 mg.
      Promethazine (PHENERGAN®), 25 to 50 mg.
      Rauwolfia root (RAUDIXIN®), 50 to 200 mg.
      Rauwolfia serpentina, alseroxylon fraction (RAUWILOID®), 2 mg.
      Rescinnamine (MODERIL®), 0.1 to 1 mg.
      Reserpine (SERPASIL®, RAU-SED®, SANDRIL®, ESKASERP®, and others), 0.1 to 1 mg.
      Thiopropazate (DARTAL®), 2 to 5 mg.
      Thioridazine (MELLARIL®), 20 to 50 mg.
      Triflupromazine (VESPRIN®), 10 to 25 mg.
   c. Muscle relaxants (all dosages are p.r.n., t.i.d.)
      Meprobamate (Miltown, Equanil), 200 to 400 mg.
      Phenaglycodol (ULTRAN®), 300 mg.
      Zoxazolamine (FLEXIN®), 125 to 250 mg.
   d. Ataraxics
      (Unless there are reasons to the contrary, it is recommended that the intensive treatment dose be reached by the end of the first week. Three months is the minimal period for an adequate clinical trial.)

	Intensive treatment dose	*Maintenance dose*
Reserpine (Serpasil, Rau-Sed, Sandril, Eskaserp, etc.)	8 to 15 mg. daily	3 to 5 mg. daily
Deserpidine (Harmonyl)	8 to 15 mg. daily	3 to 5 mg. daily
Rescinnamine (Moderil)	8 to 15 mg. daily	3 to 5 mg. daily
Acepromazine (Notensil)	75 to 300 mg. t.i.d.	25 to 50 mg. b.i.d. or t.i.d.
Chlorpromazine (Thorazine)	150 to 500 mg. t.i.d.	50 to 100 mg. t.i.d.
Fluphenazine (Permitil, Prolixin)	2 to 16 mg. t.i.d.	2 to 8 mg. b.i.d. or t.i.d.
Mepazine (Pacatal)	100 to 150 mg. t.i.d.	50 to 100 mg. t.i.d.
Methoxypromazine (Tentone)	300 to 400 mg.	100 to 200 mg. b.i.d. or t.i.d.
Perphenazine (Trilafon)	2 to 16 mg. t.i.d.	2 to 8 mg. b.i.d. or t.i.d.
Prochlorperazine (Compazine)	50 to 150 mg. t.i.d.	25 to 50 mg. b.i.d. or t.i.d.
Promazine (Sparine)	200 to 600 mg. t.i.d.	50 to 100 mg. b.i.d. or t.i.d.
Thiopropazate (Dartal)	20 to 30 mg. t.i.d.	5 to 15 mg. b.i.d. or t.i.d.
Thioridazine (Mellaril)	200 to 300 mg. t.i.d.	20 to 60 mg. b.i.d. or t.i.d.
Trifluperazine (STELAZINE®)	10 to 20 mg. t.i.d.	1 to 10 mg. b.i.d. or t.i.d.
Triflupromazine (Vesprin)	50 to 200 mg. t.i.d.	25 to 50 mg. b.i.d. or t.i.d.

   e. Undetermined
      Azacyclonol (FRENQUEL®), 20 to 200 mg.

TABLE 2

CLASSIFICATION OF SPECIFIC PSYCHOPHARMACEUTICALS* *(Continued)*

Benactyzine (SUAVITIL®), 1 to 3 mg.
Phenyltoloxamine (P.R.N.), 200 to 2400 mg.

2. Psychoactivators
   a. Psychomotor stimulants
      Dextro-amphetamine (DEXEDRINE®), 5 to 15 mg.
      Methamphetamine (METHEDRINE®, DESOXYN®, and others), 5 to 15 mg.
      Methylphenidate (RITALIN®), 5 to 10 mg.
      Pipradrol (MERATRAN®), 1 to 2.5 mg.
   b. Psychostimulants
      Imipramine (TOFRĀNIL®), 25 to 150 mg.
      Deanol (DEANER®), 20 to 100 mg. per day
   c. Psychic energizers
      Iproniazid (MARSILID®), 10 to 150 mg. per day
      (For severe depressions, an initiating dose of 50 mg. t.i.d. is recommended. Dose should be progressively cut in half on a weekly basis once improvement is established. Maintenance dose may not be necessary or may range from 5 to 10 mg. a week to 50 mg. or more a day.)
      Phenelzine (NARDIL®), 30 to 120 mg. (initial dose, 60 to 120 mg.)
      PIH (CATRON®), 3 to 24 mg. (initial dose, 12 to 24 mg.)
      Nialamid (NIAMID®), 25 to 250 mg. (initial dose, 75 to 150 mg.)
      Isocarboxazid (MARPLAN®), 10 to 50 mg. t.i.d.
3. Psychotomimetics
   a. Hallucinogens
      Lysergic acid (LSD)
      Mescaline
      Harmine
   b. Cataleptogenics
      Bulbocapnine
   c. Euphoriants
      Cocaine
      Psychomotor stimulants and psychostimulants in large doses
   d. Chronoleptogenics
      Mescaline
      Opium
      LSD
   e. Depressants
   f. Disinhibitors
      Intravenous barbiturates
   g. Confusants
      Bufotenin

*Obviously, not all psychopharmaceuticals are included. Those listed are the ones with which I have had personal experience.

Of even greater importance, certain of the combinations produce therapeutic results that neither of the agents could produce alone.

It is still my opinion that the combination of *Rauwolfia* derivatives and a phenothiazine is the most effective preparation in the overall treatment of the disturbed patient with either chronic or semichronic schizophrenia. Utilization of a psychic energizer along with a phenothiazine derivative seems to open possibilities for treatment of the agitated depressions, the withdrawn psychotic patient, and those with other syndromes for which neither drug alone seems to suffice.

Other combinations are too numerous to itemize. A distinction should be drawn between combinations capable of producing therapeutic results that could not be produced by either drug alone and adjunctive medication that serves primarily to rectify the side effects of some other pharmaceutical.

Some Convenient Rules of Thumb

Both in evaluating the clinical literature and in judging what to expect in terms of your own patients, there exist a number of indexes which are usually so well known by those in the field that they are never mentioned, and

therefore they occasionally come as a valuable surprise.

As a rule, the longer the duration of illness the more prolonged the treatment must be for adequate clinical trial. This is particularly true in regard to the ataractic drugs; although initial sedation and some lessening of psychopathology may be evident within the first weeks, the full benefits of treatment sometimes are not achieved until after as long as two years. In a case of long standing, certainly any trial of treatment lasting less than three to six months cannot be regarded as sufficient.

The incidence of both side effects and favorable therapeutic response, particularly with the ataraxics, is markedly greater in women than in men. Side effects of virtually every type occur two to three times as frequently in women, so that in evaluating the relative usefulness of different compounds one must consider the sex of the patients. A study of male subjects will show a lower incidence of side effects than will one of female subjects. On the other hand, therapeutic response is slightly better in the women. A variety of sociologic, psychologic and biochemical factors enter to some degree in creating this curious state of affairs, and anything resembling a full discussion of it would easily occupy an entire article.

As a rule, but with some exceptions, within a specific category of pharmaceuticals the greater the potency of the drug on a milligram-for-milligram basis the fewer are the side effects, although occasionally those side effects which do occur tend to be more marked than those seen with less "concentrated" preparations. As elsewhere in medicine, the real "payoff" is the therapeutic index, i.e., the therapeutically effective dose divided by the side effects, and one should not be led astray simply because compound A requires only half the number of milligrams of compound B.

Therapeutic Indications for a Psychiatrist

Please read.

The psychiatrist should be utilized exactly as should a medical specialist in any other field. Due to a number of factors, some of them concerned with the nature of psychiatric treatment but others arising purely from historical accident, there has been at times almost an estrangement between the psychiatrist and some of his medical colleagues.

The introduction of the psychopharmaceuticals has already acted favorably in strengthening the relationship between psychiatry and other branches of medicine. There is hardly a medical practitioner in the country who has not prescribed the drugs in one form or another, and all are eager to learn as much about their appropriate use as possible. At present, in contrast to the not too distant past, the meetings on psychiatric subjects are usually the best-attended lectures or demonstrations of the year.

It is now possible for the psychiatrist to handle at least a portion of his patients with primarily pharmaceutical treatment, and consequently he is able to see two or even three patients an hour and to reduce his fees to a level commensurate with those of other specialists. In cases in which intensive psychotherapy is indicated, just as when major surgery is necessary, the time and skill of the physician must be appropriately rewarded. In cases of "minor" psychiatry the family physician very frequently is able to handle the problem once he has been reassured as to diagnosis and possibly advised as to appropriate treatment. More and more, the psychiatrist is being called in as a consultant or patients are referred for diagnosis and then returned to the referring physician with appropriate recommendations. The establishment of psychiatric units or wings in general hospitals has helped to place the psychiatric patient (and his physician) on a par with other medical groups and in addition has made the psychiatrist available for consultation in regard to patients hospitalized primarily because of other disabilities.

In summary, then, the uses of the psychiatrist are the same as those of any other specialist: (1) handling of cases beyond the therapeutic skill of the referring physician; (2) referral and recommendations for treatment when diagnosis or regimen is in doubt; (3) consultation as to whether some somatic problem has psychologic aspects for which the

psychiatrist can suggest a suitable method of treatment.

Side Effects and Their Management

Drugs with any degree of potency almost invariably act at multiple sites and therefore, in addition to accomplishing the specific therapeutic objective, may produce other reactions. The obvious ways to manage these side effects are to reduce or eliminate the medication, to provide adjunctive medication to reduce or eliminate the side reactions, to substitute another medication which has the same beneficial effect without the specific side effect in that particular patient, or to get the patient to accept the fact that the specific side effect is inevitable and to learn to live with it during the period of treatment.

Irreversible side effects (except in the cases of the rare fatalities) are virtually unknown. Therefore, one can safely assure the patient that whatever it is that is bothering him will almost certainly clear up at the termination of treatment, if not before. With the more potent preparations available at present, some of the side effects appear almost inevitable. I believe it is a wise practice to warn the patient of the probable occurrence of the most frequent of these side effects and to tell him how they can be managed. Then, if the side effects occur, the patient is less alarmed than he would be otherwise, and if they do not appear no great harm has been done. If the patient presses for details as to degree of severity and discomfort, it seems wise to indicate the actual range but to stress the high degree of individual variability, indicating, as is the case, that in most instances the side effects are more annoying than either painful or serious. Unless one chooses to resort to a printed list, it is well to emphasize only the most likely side effects, since in addition one should underscore those signs or symptoms which are possible indicators of the serious side reactions and should be reported immediately. Illustrations of the common side effects would be nasal stuffiness for the *Rauwolfia* group, constipation and dryness of the mouth with the phenothiazines, and extrapyramidal symptoms for both groups of drugs. The dry, scratchy throat which may be an indication of agranulocytosis or leukopenia (with some of the phenothiazines) should be emphasized, since the patient may otherwise regard it as an unrelated and not too uncomfortable occurrence unworthy of mention. The clinical evidences of jaundice usually are sufficiently dramatic so that the patient need not be requested specifically to bring them to attention. The general opinion of most clinicians and investigators is that laboratory tests, unless done on a daily basis, are of relatively little value in detecting prodromata of most of the side effects.

The usual range of reactions including nausea, vertigo, skin manifestations, and so on may occur with almost any of the psychopharmaceutical preparations, and except when the ataraxics and the psychic energizers are being administered they should be managed by the customary procedure of withdrawal and substitution of some other compound. The side effects discussed in detail in the succeeding outline are those commonly seen with the ataraxics and psychic energizers and are *not* an indication for discontinuance or even reduction of medication, except as noted. Once a specific course of treatment has been started, it should not be interrupted short of a minimal three months' trial unless there are very serious reasons or therapeutic success is achieved.

Physiologic side effects which may occur with any ataraxic—1. Reduced resistance to intercurrent conditions (including infections). Management: Closer attention than usual with administration of larger doses of other pharmaceuticals as indicated.

2. Drowsiness. Management with amphetamines or similar compounds.

3. Weakness or fatigue. Management: Psychomotor stimulants.

4. Extrapyramidal symptoms. Antiparkinsonian medications such as COGENTIN®.

Note: Extrapyramidal symptoms are not a reason for reducing dosage or discontinuing treatment.

5. Disturbances of vision. Use of local agents or corrective glasses during the period of treatment.

6. Edema. Diuretics including DIURIL®, DIAMOX®, etc.

7. Menstrual irregularities. Diuretic agents at times are effective. Endocrine preparations should be avoided.

8. Weight changes. Use of anorectic agents.

9. Hypotension. Psychomotor stimulants or a combination of 0.01 gr. atropine and ⅜ gr. ephedrine t.i.d.

Psychologic side effects—1. Depression. Psychomotor stimulants, glutethimide (Doriden) or psychic energizers in unusual cases or imipramine (Tofrānil).

2. Anhedonia. Psychomotor stimulants, glutethimide (Doriden) and imipramine (Tofrānil); particularly useful are amine oxidase inhibitors such as iproniazid (Marsilid), Catron, phenelzine (Nardil), and nialamid (Niamid).

3. Suicidal tendency. Same management as for anhedonia, with electroshock in the emergency cases.

4. Changes in sexual function. Change to a different but related preparation if function is impaired.

5. Dreams. Glutethimide (Doriden) occasionally is useful.

6. Insomnia. Glutethimide (Doriden) or methanesulfonate (Cogentin).

7. Lethargy, retardation and withdrawal. Addition of psychomotor stimulants, psychostimulants or psychic energizers.

8. Restlessness, agitation and turbulence. Methanesulfonate (Cogentin), glutethimide (Doriden) and, in extreme cases, hyoscine. It should be noted that a period of this type is normal in the course of treatment and is definitely not an indication for withdrawal or reduction of medication.

Side reactions peculiar to Rauwolfia—1. Flushing. Transient; no treatment needed.

2. Nasal stuffiness. Local decongestants.

3. Bradycardia. Psychomotor stimulants if extreme.

4. Gastrointestinal symptoms. Cogentin or other anticholinergics.

5. Ptyalism. Cogentin or related antiparkinsonian compounds.

Side effects of phenothiazines—1. Gastrointestinal reactions including constipation. Saline cathartics recommended.

2. Dryness of the mouth. Lozenges.

3. Dermatologic reactions. Lotions containing para-aminobenzoic acid to protect against sensitivity to sunlight, which occurs with some of the phenothiazine derivatives.

4. Jaundice. Adequate hydration as a preventive; supportive treatment if it occurs.

5. Leukopenia and leukocytosis. Customary management.

Side effects of psychic energizers—1. Potentiation of other medications. Great care should be taken, since many other medications are increased in potency from 5 to 10 times when a patient is receiving certain of the amine oxidase inhibitors.

2. Hepatotoxicity. Most hepatitis is due to infectious hepatitis. As a preventive measure, if viral infection is present among immediate contacts, the drug should be discontinued. Whether any of these drugs actually cause hepatitis is not yet determined, since the condition (if it exists) is indistinguishable from that caused by a virus.

3. Hypotension. Psychomotor stimulants.

4. Neuralgias and paresthesias. Addition of 25 to 50 mg. pyridoxine (vitamin B_6) daily.

5. Changes in bowel habits. Saline cathartics or enema.

6. Changes in sexual function. Transfer to another amine oxidase inhibitor or psychic energizer. This side effect can be used for treatment in some cases of ejaculatio precox.

7. Weight changes. Anorectic agents and dietary control.

8. Edema. Diuril, Diamox, etc.

9. Insomnia. Adjustment of the patient's thinking to realization of the fact that less sleep is needed. Barbiturates and other medications should definitely be discouraged.

What Can Be Done to Help the Medical Practitioner Improve His Skills

Psychiatric concepts are so complex that most physicians, anticipating no great need for them in future medical practice, either tended to neglect them in medical school or have long ago forgotten them since there was little or no occasion to put them to practical use. As a consequence it is more difficult for the practicing physician to evaluate literature in this field, and his diagnostic ability is less

sharp in these cases than it is in most other medical areas. Add to this a reluctance to refer patients for psychiatric consultation, and certain difficulties are bound to ensue: A higher than average percentage of patients will be misdiagnosed and consequently will not receive adequate treatment. The drugs may be used too sparingly or too enthusiastically with fewer successes and more side reactions. Many psychiatric conditions require prolonged treatment before therapeutic response can be expected, and the physician may become impatient, shift from one drug to another, and abandon treatment prematurely. In other cases, treatment may be unnecessarily and untherapeutically prolonged. Fear of side reactions may induce a physician to use a less potent drug when adjunctive medications might be available to reduce the side reactions of an adequate preparation and when knowledge and experience with such side reactions could be used to reassure the patient of their temporary necessity. Contrariwise, prolonged use with disregard of side effects may also lead to therapeutic failure and complications.

The solution is perfectly obvious but difficult to achieve: education of the physician in respect to drug usage and psychiatric diagnosis. This would enable him to determine an appropriate treatment and know when referral to a psychiatrist for diagnosis, consultation or treatment is indicated. What makes this difficult to achieve is that for many physicians a new or forgotten area of medical knowledge suddenly becomes a necessity. In the midst of a busy practice it is extremely difficult to devote the time and energy necessary or to make the financial sacrifice required to bring this about. The medical societies have made a valiant effort in this direction, but one or two lectures a year at the scientific meetings cannot provide the systematic knowledge needed. The medical journals have included more and more articles on psychiatric problems, but without the requisite background these articles may be subject to misinterpretation. Some of the pharmaceutical houses have tried to provide various types of assistance in furnishing the practitioner with the appropriate background. None of these efforts, separately or together, seem likely to provide what is necessary. The one most sensible program advocated is that the National Institute of Mental Health, under the direction of the American Psychiatric Association, should provide systematic lectures or refresher courses to be financed by federal funds. A start has been made in this direction, but the program needs very definite expansion if it is to achieve its purpose. In the meantime, when in doubt, the diagnostic and therapeutic abilities of the psychiatrist should be utilized.

Disorders of the Cervical Spinal Cord in Older Patients

FRED PLUM*

University of Washington School of Medicine, Seattle

Cervical spondylosis with compression of the spinal cord is the most common producer of spastic paraparesis of the lower extremities in middle-aged and elderly persons. Other conditions which are likely to produce this picture, often combined with impaired function of the arms, are subacute combined degeneration, amyotrophic lateral sclerosis, and multiple sclerosis. Features which are important in differential diagnosis are listed.

Intermittent cervical traction produces at least temporary clinical improvement in most cases of cervical spondylosis, and sometimes the degree of improvement is remarkable in view of the underlying abnormality of bone and cartilage.

FRED PLUM

SEVERAL diseases appearing during the middle or older years of life produce insidiously painless, stiff weakness of the legs, often combined with some impairment of strength in the hands. Particularly likely to produce these symptoms are cervical spondylosis with spinal cord compression,[1,2] subacute combined degeneration (vitamin B_{12} deficiency), amyotrophic lateral sclerosis, and multiple sclerosis. Tumors of the cervical spinal cord also cause the picture. Syringomyelia usually evinces itself at a younger age. multiple sclerosis. Tumors of the cervical processes are similar, the practitioner sometimes has difficulty in deciding among them. However, in most instances careful clinical examinations supplemented by a limited number of laboratory studies will identify the illness accurately.

Table 1 lists some of the important features in the differential diagnosis of spastic paraparesis in older patients. Clinically the key to accurate diagnosis lies in close attention to a history of previous neurologic episodes, the demonstration of abnormalities above the neck level, the presence of sensory changes and their type, and involvement of excretory sphincters. Lumbar puncture, x-rays of the cervical spine, and blood counts usually are

*Division of Neurology, Department of Medicine, University of Washington School of Medicine, Seattle, Washington.

required as the minimum of laboratory aids to secure diagnosis. Occasionally, cervical myelography and vitamin B_{12} absorption studies must be employed.

Cervical Spondylosis

In our experience, impairment of function of the spinal cord secondary to spondylosis of the cervical spine is by far the most common producer of spastic paraparesis of the lower extremities in middle-aged and elderly persons. Clinically, two syndromes can be identified. One is characterized by gradually developing spastic paraparesis in the lower extremities alone, and the other is marked by paraparesis in the legs plus changes in the arms, including selected weakness, wasting, reflex diminution, and sensory impairment. The disease is often marked by long periods of symptomatic stability. A third type of distribution also occurs occasionally in spondylosis, with involvement of nerve roots affecting the arms alone, without any involvement of the spinal cord. This distribution is more characteristic of acute disease of the disks, but it sometimes occurs with osteophytes at the intervertebral foramens. The absence of spinal cord changes prevents confusion with the other illnesses considered here.

The pathogenesis of cervical spondylosis is related to degenerative disease of the joints and consists of gradual degeneration and posterior protrusion of cervical intervertebral disks and an associated osteophytic reaction of adjacent vertebrae (figures 1 and 2). The protruded disk hypertrophies and calcifies, forming a hard transverse bar or boss which narrows the anteroposterior diameter of the spinal canal and eventually compresses the spinal cord or interferes with its blood supply. This medially placed protrusion accounts for the spastic paraparesis and sensory loss in the lower extremities. Several disk levels may be involved. Often the spondylotic bar may extend or arise laterally within the spinal canal, encroaching on the spinal roots where they enter the intervertebral foramens and narrowing the foramens themselves. Osteophytes extend directly into the foramens from the adjacent uncovertebral (anteromedial) and apophyseal (posterolateral) articulations. Adhesions within the foraminal root sleeve may further limit the mobility of the roots,[3] increasing their susceptibility to trauma during movement of the neck and arms. Such root involvement leads to the localized motor and sensory impairment so often found in the upper extremities.

The most frequent anatomic sites of advanced spondylosis are the disk levels of C3-4, C4-5, C5-6 and C6-7, with alterations at the C4-5 and C5-6 levels most often producing symptomatic changes.

The relative contributions of aging and trauma in causing spondylosis are difficult to assess. The intervertebral disks progressively lose their hydration and elasticity with advancing years, and this increases the susceptibility of the adjacent vertebral bodies to wear and tear during unusual neck mobility. Many patients give a history of one or more episodes of direct trauma to the head or neck, but such a history is far from unusual among persons without symptomatic spondylosis. Only rarely has a history of trauma immediately preceded symptoms in our experience, and in these cases it may have been merely coincidental.

Clinical story and findings—Most patients with spondylosis are in their 50s or 60s when symptoms begin. The illness is rare in persons less than 45 years of age, and affects men more often than it does women. Although presenting complaints may be referable to either the arms or the legs, neurologic abnormalities in the lower extremities are the most predictable features of the illness. One leg or both may "give out" or "buckle" when fatigued. There may be so much spasticity that shuffling replaces normal walking. Occasionally, "leg jumping" (flexor spasm) develops in some patients, but it seldom is prominent. Walking on rough terrain or descending stairs tends to be particularly difficult, partly because of associated sensory losses. Examination of motor function is consistent with these complaints. Bilateral spasticity of the lower extremities is present, ranging from mild to marked, and there is weakness, particularly about the knee and ankle, with hyperactive

TABLE 1

DISEASES PRODUCING WEAKNESS AND WASTING IN ARMS COMBINED WITH SPASTICITY IN THE LEGS

	AMYOTROPHIC LATERAL SCLEROSIS	CERVICAL SPONDYLOSIS	SUBACUTE COMBINED DEGENERATION	MULTIPLE SCLEROSIS	CERVICAL SYRINGOMYELIA	CERVICAL EXTRAMEDULLARY NEOPLASM
Usual onset (age, years)	25 to 70; usually over 50	Over 50	Over 45	Under 40	Under 40	Any age
Pain	Absent or mild; muscular in neck	Rarely prominent; neck muscle or root	Absent	Absent	Absent	2 to 4+; radicular and local
Paresthesias	Absent	Hands, radicular, rarely prominent	Feet, hands or both, 3 to 4+	Absent	Absent	Radicular
Fasciculations	Generalized	Arms only, restricted to myotomes	Absent	Absent	Arms only	Arms occasionally
Cranial nerve changes	Fasciculations of tongue, jaw jerk	Absent	Absent (rare anosmia, optic atrophy)	Optic atrophy, nystagmus, jaw jerk, etc.	Absent	Absent
Sensory changes, arms	Absent	Usually minimal and in root distribution (dermatome)	Glove, with deep sense loss predominant	Tract type, not peripheral or radicular	Dissociated pain and temperature, often glovelike	Radicular
Sensory changes, legs	Absent	Tract type, vibratory loss exceeds position loss, superficial loss rare	Both peripheral and spinal tracts, position loss often pronounced	Tract type, any modality	Tract type, deep sensibility, sacral sparing of pain	Tract type, pain loss prominent
Bowel and bladder involvement	Absent	Absent or very late	Relatively early with atonia, due to position loss	Spastic, frequent and early	Usually late	Frequent but late
Cerebrospinal fluid	Negative	Modest protein elevation (50-80 mg.)	Negative	Many have cells, alteration of colloidal gold curve, modest protein change	Negative	Significant protein elevation, block
X-ray, cervical spine	Negative	Spondylosis and intervertebral foraminal encroachment by osteophytes	Negative	Negative	Negative or associated developmental anomaly	Pedicle widening, foraminal enlargement

patellar and Achilles tendon stretch reflexes and abnormal plantar responses.

As a rule, sensory symptoms in the legs are present but not prominent. Patients may state that the feet feel "wooden" or difficult to locate in the dark; seldom do they tingle, as do the extremities in combined system disease. Three of our patients complained prominently of burning in the soles of the feet, a symptom which originally suggested local circulatory insufficiency. However, there was no evidence of arterial disease and the burning disappeared after cervical traction therapy, concomitantly with other neurologic improvement. Contrasting with the paucity of sensory complaints, testing of the lower extremity al-

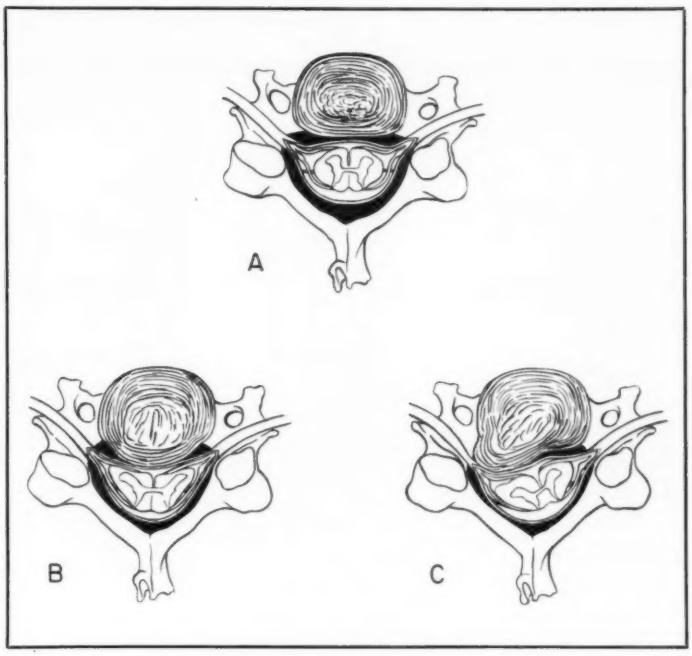

FIGURE 1. The relative positions of medial (B) and lateral (C) posterior disk protrusions to the spinal canal. A. Normal relationship of the intervertebral disk, seen from above, to the cervical vertebra. Note that in C, not only is the cord compressed and displaced from its lateral attachment to the dentate ligament, but the nerve root is also compressed as it enters the intervertebral foramen.

most always demonstrates altered deep sensibility, with vibratory sensation usually more impaired than position sense. Thus, even when vibratory sensation is reduced or absent up to the iliac crests, position sensation usually is no more than mildly impaired in the toes, and the superficial sensations of touch, heat and pain almost never are impaired unless spinal damage is unusually far advanced.

Bladder and bowel incontinence or retention is rare in cervical spondylosis, so rare, in fact, that if serious sphincteric disturbances occur in the absence of very advanced spinal cord damage or local urinary tract disease one should suspect parenchymal spinal cord disease such as multiple sclerosis or tumor.

Neurologic changes in the upper extremities in cervical spondylosis vary considerably from patient to patient depending on the level of compression of the spinal cord and on which, if any, of the spinal roots are involved. Unless there is direct root damage, hyperactive reflexes may be the only clinical findings in the upper extremity to implicate a lesion of the cervical spinal cord. When the cervical roots are involved, localized sensory and motor defects having a radicular (nerve root) distribution become superimposed on the cord signs. Frequently there is asymmetrical weakness of the arms combined with localized muscular wasting, and fasciculations often are found in the muscles served by the injured nerve root. Stretch reflexes generally are reduced in the segment of the arm directly affected by the root lesion, while reflexes in immediately adjacent segments commonly are hyperactive due to the associated involvement of the spinal cord. Sensory symptoms may include dull aching in the neck, occasionally with a history of recurrent "wryneck." Radiation of dull, aching pain into the shoulder is fairly common, and vague tingling or numbness may radiate in nerve root distribution into one or more fingers. Occasionally, percussion of the cervical spine or sudden flexion of the head may produce radiating paresthesias into the arm or "electric shock" paresthesias radiating down the back to the legs.

General laboratory studies yield negative results in spondylosis. Lumbar puncture often shows modest elevations in protein content of the cerebrospinal fluid (up to 75 mg. per cent) and may reveal a manometric block when the jugular veins are compressed with

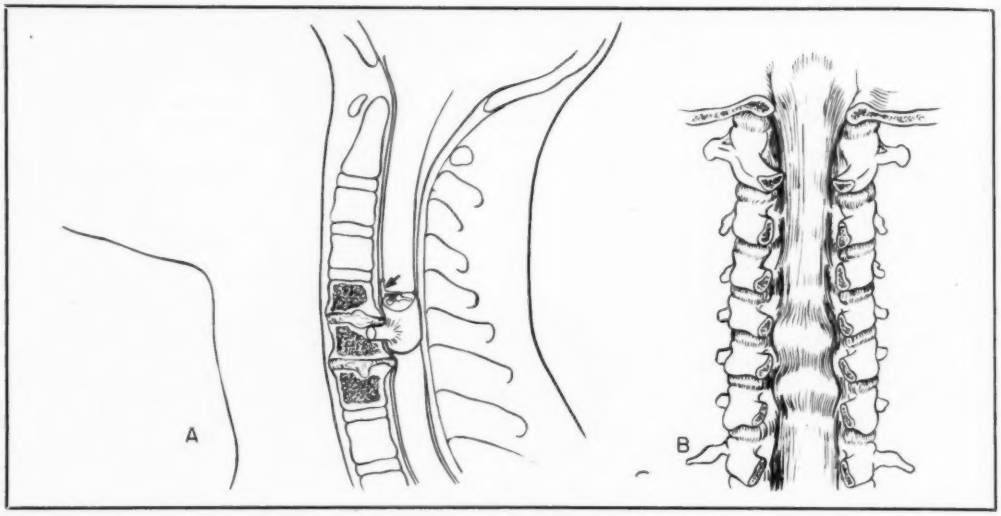

FIGURE 2. Diagrammatic presentation of cervical spondylosis at the C4-5 and C5-6 levels. A. Sagittal section showing the posterior protrusion of the disk with associated lipping and posterior osteophyte production of the adjacent vertebral bodies. The arrow points to the anterior spinal artery, illustrating its vulnerable position as cord compression develops. B. The anterior wall of the spinal canal, showing the posterior and posterolateral bulging typically encountered in advanced spondylosis.

the head in full extension. (Because of the damage of local vascular decompensation and subsequent swelling of the cord, jugular compression never should be attempted except as an immediate preoperative procedure if spinal cord tumor with complete block is suspected.) There is no abnormality of colloidal gold curves or gamma globulin in the cerebrospinal fluid in cervical spondylosis.

Plain x-rays of the cervical spine usually show evidence of advanced degenerative disk disease, usually with adjacent formation of posterior osteophytes and foraminal narrowing (figure 3). Correlation of the degree of abnormality on plain films of the spine and the intensity of neurologic symptoms is poor, however, as many patients have severe degenerative changes in the cervical spine without neurologic deficit. Therefore, although normal x-rays of the cervical spine are strong evidence against the diagnosis of spondylosis, abnormal plain x-rays cannot alone be relied on for diagnosis when clinical findings are equivocal. When differential diagnosis of spinal cord lesion is doubtful, myelograms (PANTOPAQUE®) should be made to outline soft-tissue protrusions and adjacent osteophytic formation not visible on plain x-rays.

Treatment—Most patients benefit from conservative management. Those who have been doing heavy physical work often are improved if they change to more sedentary employment. Intermittent cervical traction produces at least temporary clinical improvement in most instances, and the neurologic progression halts in a high percentage.

It is our practice when treating cervical spondylosis to rely exclusively on counterweighted head halters for traction. Supporting collars seldom are beneficial. Initial traction is applied with the patient at bed rest, and particular care is taken to distribute the pull evenly between the chin and the occiput. Nine to 12 lb. of weight is used, with traction applied alternately throughout the day for two hour intervals. Nocturnal traction also is attempted but is discontinued if the patient has difficulty sleeping. Muscular relaxants (mephenesin, FLEXIN®, SOMA®) sometimes are given, although their benefit is questionable. Supine traction is continued for two to seven days, depending on clinical response, and

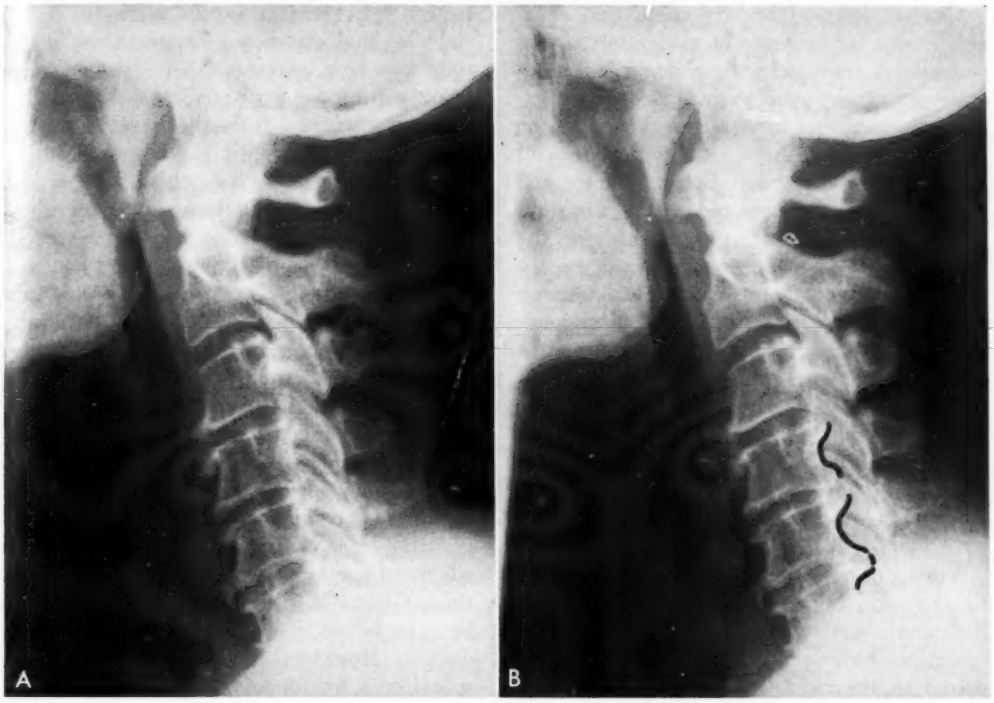

FIGURE 3. Lateral x-ray of the cervical spine of patient with spondylosis. A. Plain film. B. Retouched film to outline soft-tissue shadows seen on original films and to show narrowing of spinal canal.

gradually replaced by erect traction with the patient sitting in a firm straight chair. Again, particular care is given to adjusting the traction vertically. For sitting traction the counterweights are gradually increased to 25 to 30 lb. and the duration of traction is reduced to half-hour periods. Two to three such half-hour periods daily are then continued indefinitely, the patient installing his own apparatus at home.

In view of the underlying abnormality of bone and cartilage, it is remarkable how much some patients improve with traction therapy. The following brief case report gives an example of this.

Case report—A 64 year old man was admitted to the University of Washington Hospital complaining that his feet had "burned" for two months and that his right leg had been weak for two years. He worked as the operator of a heavy truck, and had always worked vigorously, but recalled no specific neck trauma.

Six years earlier he had noted tingling in the right third and fourth fingers, and this had persisted unchanged. Two years earlier he had noted easy stumbling on rough ground, and since that time his legs had gradually become stiffer. His right leg occasionally buckled when he walked, and he noted gradually increasing right foot drop. He had difficulty descending stairs and in being certain of the position of his right foot. Two months prior to admission, the sole of the right foot felt hot, particularly when he stood or touched something with the foot, and in the month immediately preceding admission he also noted burning sensations in the sole of the left foot.

He had not had headache, cranial nerve symptoms, neck pain, or trouble with bowel or bladder.

General physical findings were unremarkable except for evidence of moderately severe generalized arteriosclerotic changes and moderate pulmonary emphysema. Neurologic examination showed bilateral weakness of the triceps muscles in the arms with weakness of the right supinator group. Both the biceps and the triceps reflexes were reduced on the right side. Although the arms were thin for the man's size, selected wasting could not be discerned. However, there were fasciculations in the right triceps muscle. Superficial abdominal reflexes were present but reduced on the right. Both lower extremities were mildly spastic, particularly the right, and there was moderate weakness throughout the right leg, increasing in degree distally. Knee and ankle jerks were increased, particularly in the right leg, and bilateral extensor plantar responses were found.

Vibratory sensation was absent to the midtibial region bilaterally, and reduced to the iliac crest, particularly on the right. Position sensation, however, was only minimally impaired on the right toes, and this and other sensations were normal elsewhere.

The cerebrospinal fluid showed no manometric block with the head in flexion or extension. The fluid was clear and acellular and contained 56 mg. of protein per hundred cubic centimeters. X-rays of the cervical spine (figure 3) showed straightening of the normal cervical curve, anterior osteophytes from C3 to C6, and posterior osteophytes adjacent to the disks at C3-4, C4-5 and C5-6. The anteroposterior diameter of the spinal canal was reduced to 11 mm. (normal, 15 mm.) at the C5-6 level. Oblique films showed intervertebral foraminal encroachment by osteophytes at the C5-6 and C6-7 levels, particularly on the right.

Supine traction with a cervical halter was started, using 12 lb. of weight and with traction applied two hours out of three and during the night. Within 48 hours the burning sensations in the feet were reduced to negligible proportions. Sitting traction using 30 lb. of weight was initiated after 72 hours. Because of the patient's age, ambulation was begun on the fifth day, at which time he noted subjective improvement in the strength of his right leg and significant improvement in the right foot drop, and was able to descend stairs unassisted for the first time in several months. He was dismissed from the hospital on the tenth day and has continued the use of sitting traction at home, one hour three times a day. Three months after the treatment in the hospital, burning in the feet had not returned, the improvement in walking strength had continued, and further regression of the right foot drop was noted. Position sensation in the right foot was nearly normal, but the sensory loss in the right hand had not diminished. The remainder of the examination did not reveal significant changes in his condition.

Indications for surgical treatment—It is difficult to give specific indications for surgical treatment in cervical spondylosis because complicating medical problems associated with advanced age so often constitute contraindications. Generally speaking, surgery usually can be expected to arrest the progression of the disease. However, marked improvement in spinal cord function is unusual, since procedures which go beyond decompressive laminectomy and cutting of the dentate ligaments carry a high risk of morbidity. Well-documented steady progression of cord signs threatening to produce incapacitation is certainly an indication for surgery if improvement is not seen following traction. Surgery is particularly to be recommended if the neurologic progression is rapid. In the arms, progressively advancing severe wasting, weakness or sensory loss which fails to respond to traction similarly indicates the consideration of foraminal decompression. Both in the lower and in the upper extremities, motor improvement is more likely after operation than is sensory return.

Differential Diagnosis of Conditions Causing Spastic Paraparesis in Older Patients

Amyotrophic lateral sclerosis—Amyotrophic lateral sclerosis frequently has its onset in the middle and older years of life, sometimes with the combination of weak arms and spastic legs. Several clinical features help to

distinguish the disease (table 1). Frequently there is dysarthria or dysphagia, placing neurologic lesions clearly above the neck level. Muscular fasciculations, although often asymmetrical, usually become generalized rather than localized to motor root segments in the arms as in spondylosis. Frequently, fasciculations can be observed in the tongue as well as in the trunk and lower extremities. Sensory changes are lacking in amyotrophic lateral sclerosis, and cervical roentgenologic abnormalities are either absent or only a coincidental finding. The cerebrospinal fluid is normal. Only rarely is the clinical picture so unclear that myelography is required for the diagnosis.

Subacute combined degeneration—Clinically, the neurologic manifestations of vitamin B_{12} deficiency usually consist initially of a subtle peripheral neuropathy with prominent tingling paresthesias which are usually symmetrical and glovelike or stockinglike in distribution. (In spondylosis, paresthesias are usually confined to the arms and have an asymmetrical and radicular rather than a peripheral distribution.) Although position and vibratory changes are the most prominent sensory changes in combined system disease, distal loss of touch and pain sensation usually can be found by the time that changes in the spinal cord lead to spasticity of the lower extremity. Loss of position sense in the lower extremity is more prominent in combined system disease than in spondylosis. Muscular fasciculations are absent, and although the lower extremities become spastic and abnormal reflexes appear as spinal cord degeneration ensues, the accompanying peripheral neuropathy usually results in a loss of ankle jerks. Because of damage to the afferent neural arc, urinary retention accompanies advanced vitamin B_{12} deficiency. (Frequently there is mild impairment of cerebration, producing mild to moderate defects of memory and attention accompanied by a loss of a sense of well-being.) There are no abnormalities in the cerebrospinal fluid or on roentgenograms of the cervical spine in subacute combined degeneration.

The diagnosis of vitamin B_{12} deficiency is suggested in most instances by the finding of gastric achlorhydria plus a macrocytic anemia with a reticulocytic response to parenteral injections of vitamin B_{12}. The untreated bone marrow usually is megaloblastic by the time neurologic symptoms develop. In the rare instances in which neurologic deficits precede anemia or in which folic acid therapy has prevented anemia, radioactive B_{12} absorption studies[4] or determination of serum levels of B_{12}[5] may be required. Accurate diagnosis is imperative, for treatment must be continued permanently to prevent relapse. Conversely, erroneous treatment of spinal cord compression by vitamins can have tragic consequences.

Multiple sclerosis—Multiple sclerosis frequently is a disease of younger persons and produces a clear story of dissemination, but sometimes presents its major symptoms with insidiously progressing paraparesis in elderly persons. As Brain and Wilkinson[6] have emphasized, moderate spondylosis, ordinarily insufficient to cause symptoms by itself, may accentuate the spinal symptoms of multiple sclerosis and be responsible for localizing progressive demyelinization at the cervical level. Recognition of multiple sclerosis is important, for surgery often accentuates the course of this disease, which otherwise may undergo long periods of remission with conservative management.

Multiple sclerosis should be suspected as the cause of spastic paraparesis when the recent or remote history shows episodes of migrating or fleeting neurologic deficits, particularly when these have affected cranial nerve function. A hyperactive jaw reflex, for example, incriminates a source of bilateral spasticity which clearly lies above the foramen magnum. Multiple sclerosis is particularly likely to produce rapidly developing and rapidly remitting paralysis in the extremities, whereas spondylosis generally runs a more insidious, less fluctuating course. Early or transient impairment of sphincteric function is more characteristic of multiple sclerosis, as are sensory defects which prominently impair stereoperception and spread themselves diffusely over an extremity or zone of the trunk. In contrast, localized root signs and symptoms

in the upper extremities almost never result from multiple sclerosis but are common in spondylosis.

The cerebrospinal fluid in multiple sclerosis often shows white cells, a finding lacking in spondylosis. Elevation of gamma globulin or an abnormal colloidal gold curve favors the diagnosis of multiple sclerosis. As stated previously, plain films of the cervical spine will be abnormal in spondylosis, but only coincidental changes will be seen in multiple sclerosis. Finally, if doubt persists after careful clinical appraisal and examination of the cerebrospinal fluid, cervical myelography may be necessary for diagnosis. Since patients with multiple sclerosis may have a relapse following myelography, however, the procedure should be used with great reservation.

Spinal cord tumor—Although spondylosis is a form of tumor, what is meant here is progressive growths caused by neoplasia rather than the process of degeneration and repair.

In older persons, spinal tumors are much less frequent than is spondylosis, although this knowledge hardly helps to diagnose the individual case. Both primary and metastatic tumors usually develop and progress more steadily and rapidly than does spondylosis. Metastases to the spine usually are readily identifiable by the destruction of bone seen on x-rays. Intraspinal, extramedullary tumors are distinguished by prominent root pain, by more restricted root involvement, and by the production of cord signs which point more clearly to unilateral damage to the spinal cord. Thus, tumor is particularly likely to be the cause of impairment of the pyramidal tract and deep sensations in one leg combined with defects in pain sensation on the opposite leg and trunk (partial Brown-Séquard syndrome). The protein level of the cerebrospinal fluid tends to be higher (frequently above 70 mg.) in cord tumor, while spondylotic signs on plain x-rays generally are lacking.

Intramedullary cervical cord tumors are very uncommon in older persons. When they arise, the initial development of spastic paraparesis combined with poorly localized neck pain or sensory symptoms may at first suggest spondylosis. However, a more rapid progression, the frequently early development of sphincteric disturbances, and the appearance of broad bands of hypalgesia and hypesthesia in the arms or upper trunk should point away from the diagnosis of spondylosis. Again, x-rays often will be helpful by failing to show spondylosis and, sometimes, by revealing widening of the vertebral pedicles. Myelography usually is diagnostic when the clinical findings are doubtful.

Syringomyelia—Syringomyelia, because it usually presents itself before the age of 35 years, seldom is confused with spondylosis, which is a disease of older groups. Rarely, cervical syringomyelic cavities are found in association with advanced spondylosis. One of our patients had such a change. Whether or not the cavity was secondary to ischemia induced by the cord compression from the spondylotic ridges was unclear, even at autopsy. The fact that dissociated sensory loss and wasting in the hands had developed first when the patient was 58 years of age suggested that the cavitation was a sequela to the bony lesion. At any rate, syringomyelia is a disease best treated conservatively and is not a contraindication to managing patients with advanced cervical degenerative joint disease as if the arthritic process were the entire cause of the neurologic deficit.

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Juvenile Delinquency; a 1960 Perspective

EUGENE I. FALSTEIN*

Chicago Medical School, Chicago

Approaches to an understanding of juvenile delinquency have been hampered by attempts to attribute it to a single cause, continued use of outmoded classifications and terms, the individual jargons of the various schools of thought in psychiatry and ancillary fields, and diagnostic generalizations based solely on symptoms. A multidisciplinary approach is becoming more and more essential to productive progress in this area. Prevention is our chief hope in eradication of the problem. We must depend on a slow kind of "immunization" that can be achieved only through attainment of maturity by a world still too full of greed, envy and hostility. The psychiatrist alone is helpless in trying to achieve this goal.

EUGENE I. FALSTEIN

Basic scientific medicine, which, whenever possible, seeks a single etiologic factor in the production of disease, finds itself beset by seemingly insurmountable obstacles in the investigative approach to mental illness with all its complexities. The symptom constellation of delinquency, in particular, because of its readily recognizable manifestations, has tempted many investigators to settle on one-sided approaches to an understanding of its cause, with a resultant plethora of etiologic claims. There has been little consideration of a total field in which most or all of the factors operate, and only relatively recently has there been a grudging tendency to concede to a multiple-factor etiology. Diagnostic generalizations based solely on symptoms have contributed to the confusion that has characterized the extensive literature on the subject.

Actually, "delinquency" is a commonly used nonpsychiatric, nondynamic term comprising many conditions varying in etiology, severity, duration and underlying egopsychopathology and springing from different levels of structure and conflict. Delinquency refers generally

*Clinical Professor of Psychiatry, Chicago Medical School; Attending Psychiatrist and Chief of Child and Adolescent Care, Institute for Psychosomatic and Psychiatric Research and Training, Michael Reese Hospital Medical Center, Chicago, Illinois.

to behavior, thoughts and feelings that tend to infringe on values, and concerns itself with disorders characterized by the lack of control of impulses, which are then "acted out." Since it is often nothing more than a symptom defense or pattern of behavior, it becomes essential to our understanding to adopt Glover's concept of a "delinquency continuum" from the normal to the abnormal.

It is now generally accepted that all "normal" personalities contain an acting-out psychopathic core. One perceives transient crises due to functional stress, as well as symptomatic reactions to oedipal conflict, sociocultural influences, group suggestibility, puberal stress and adolescent growth confusion. Delinquent symptoms may appear as defensive maneuvers designed to ward off a psychosis, as concomitants of addictions and psychoneuroses, or as natural defenses in basically healthy youngsters who are reacting to wrong handling, unhealthy living conditions, or traumatic experiences. Organic brain disease, particularly when associated with some degree of mental deficiency, may contribute to the production of delinquent manifestations by distorting ego development and functioning. Finally, there is genuine confirmed pathologic delinquency characterized by firmly established disturbances in the child's impulse system, with typical malformations of the ego, superego and ego-ideal components of the psychic apparatus.

Interpretation of delinquent behavior as such depends on a specific set of sociocultural values, and what might be so termed in one locale could well be totally acceptable in another. There are many so-called delinquency areas where nondelinquent behavior is considered abnormal.

In my opinion, Redl's classical and comprehensive descriptions of the formation and operation of the true delinquent ego and superego are the best and most thorough in the field. When one reads about his "children who hate," one is immediately impressed by his intuitive observations of these ego-warped youngsters who constitute the projected criminals of later years.

Unfortunately, nosologic confusion has been another contributing factor to the psychiatrist's dilemma. Classifications and terms which have become outmoded continue to crop up in the literature. The individual jargons of the various schools of psychiatric thought, when added to those of the ancillary fields such as sociology, anthropology and psychology, have led to general misunderstanding and actual mutual hostility. They have constituted disastrous deterrents to cooperative effort in an area where the multidisciplinary approach is becoming more and more essential to productive progress.

At one time the term "juvenile delinquency" immediately evoked the picture of a deprived, unloved child of the slums. Today we expect to encounter delinquent behavior at every socioeconomic level and are not fooled by the tendency to refer to the rich delinquent as a bad or sick child who can be sidetracked to the private psychiatrist's office instead of the detention home or reform school.

Dynamic (psychoanalytic) psychiatry, more than any other single factor, through its primary concern with individual depth psychology, has offered an explanation for the occurrence of juvenile delinquency at all socioeconomic levels. Studies of the development of the psychic apparatus, and particularly of the superego, that portion responsible for controls and discipline, readily reveal the defects and lacunae that are characteristic of the antisocial acting-out child, while demonstrating at the same time the interplay with parents and environment that eventuates in the development of these warped characters.

Many years of experience will convince one that each child must be studied on a completely individual basis from every standpoint, particularly from that of establishing a psychodynamic evaluation and formulation. It is indeed surprising to see the many basic variations in the personality development of youngsters who seem to present identical clinical pictures symptomatically.

Collaborative therapy of parents and children, when applied to the problems of delinquency, has given us greater insight into the important dynamic intrafamilial relationships than has any other method. Johnson and her co-workers have described very dramatically

and lucidly the manner in which children are more or less seduced into their antisocial acting-out behavior by the unconscious initiating, fostering and sanctioning activities of their basically corrupt parents. Others have determined the way in which specific ego defenses are set up and utilized by inconsistent mothers with unsolved oral needs that can be traced back through preceding generations. In fact, the "psychologic microscope" has enabled us to evaluate the individual's defense mechanisms in considerable detail, as exemplified by Jacobson's work which has demonstrated why acting-out appears to be regularly linked with a bent for denial, and why patients who deny show a propensity for acting-out.

Recent investigations have pointed to a disproportion in the oral needs and oral satisfactions of many infants at birth and shortly thereafter. These needs may be greater than average and may not be satisfied by any normal parent, in contrast to those cases where the need is average or even less and is not satisfied by a particular parent. It is important to remember that children will conform and control basic instinctual drives only when they receive genuine love in return. Without this love or the realization that someone really cares, there is no real incentive to exert these controls and to tolerate frustration.

Our own studies have led us to trace the character development of most true delinquents in the following fashion. Repeated lacks of satisfaction and gratification in the infant result in a persistent oral need. During the early feeding periods the child incorporates the image of a bad, depriving, rejecting mother, whether she is actually bad or is merely experienced as bad because of her failure to gratify the great oral needs of the particular child. We speak of the development of a very strict archaic superego as the result of the internalization of this mother-child transactional process. There is little differentiation between the concept of bad child and that of bad mother, but there is always a greatly lowered self-esteem in the child as a result. As he grows, it would appear that there develops in the secondary superego a definite permissiveness to mobilize and express aggression outside the home. It is as though the mother (the primary continuing object of a hate that is largely resolved during the oedipal phase of development by an increasingly strong identification with her) is saying to the child, "You may steal and hurt as long as you don't do it to me. Take those impulses elsewhere."

Characteristics of the Delinquent

It may be worthwhile to review the characteristics of the delinquent, bearing in mind, however, that the extremes which I shall depict are rarely if ever encountered, since there are always admixtures of neurotic, psychotic or perverse symptomatology that color the clinical picture.

In the sphere of conation, there is always a low level of awareness in all areas of behavior. In other words, the extreme delinquent shows little or no consideration as to whether or not an act should be performed or what the consequences may be.

In the area of cognition which embraces such autonomous ego processes as memory, perception, intelligence, fantasy and thinking, there is an awareness only of what appears to be potentially gratifying, a tendency to forget unpleasant past events, and a bent toward distortion and denial. Fantasy is relatively uncommon and when present is of the simple wish-fulfillment variety, with little relation to reality. Dreams, when revealed, are usually of the same type; thought processes are often illogical and unconventional; there is a tendency to confabulate; and magical omnipotent thinking is often in evidence. The degree of intelligence will often determine the manner in which antisocial behavior is expressed. Swindlers, imposters and various types of "con men," for example, represent the most highly intelligent category.

In the relation to and the testing of reality, there appears to be an inability to evaluate and learn from past experience or to visualize eventualities. Poor judgment and maladaptive behavior prevail, associated with confusion concerning the self and interrelationships with others.

In the handling of instinctual drives, there

appear some of the most prominent manifestations of the delinquent, namely, an attempt to gratify impulses immediately in all areas of behavior, an inability to tolerate frustration or anxiety, and a true superego defect with resultant defective controls.

In the sphere of affect or emotion, one notes the absence of tension accumulation because of the constant discharge through acting-out. Guilt and shame are prominently absent, and anxiety is minimal, primitive and transient. Depression, always present as an underlying core of the personality structure, is constantly denied and defended against. It appears regularly during successful therapy.

Among the ego defenses, massive repression, isolation and denial predominate. As a result, one observes little or no evidence of conflict.

Object relations are characterized by little or no investment emotionally in other persons or things. On the contrary, there is an overinvestment in self or in the peer group which represents an extension of the self.

Generally speaking, the antithesis of the characteristics outlined would spell out those of the neurotic child. When speaking in terms of therapy, although it may represent an oversimplification, one may say that the goal usually consists of converting the delinquent into more of a neurotic, and vice versa. Because the neurotic can foresee through treatment a diminution in tension, anxiety, conflict and depression, he more readily becomes a willing, cooperative patient. When it is realized that the delinquent must learn to experience and cope with these very same symptoms, it is not difficult to understand why he becomes an unwilling, uncooperative, elusive patient, and why, once in therapy, he is easily tempted to avoid or run away from it.

Collaborative Psychotherapy of Child and Parents

When a delinquent child is living at home, it is often essential to employ collaborative psychotherapy involving child and parents. Only in this manner can one control the extrinsic factors that provoke the child's acting-out. We know that the more or less unconscious hostile, destructive and rejecting attitudes of deceitful, corrupt, guilt-ridden parents continue to operate repetitively in the direction of stirring up the child's acting-out behavior. The delinquent, who is characteristically tricky, scheming and corrupt, becomes an intricate part of a mutually gratifying relationship. It is frequently good policy therapeutically to break up such an association by removing the child to a new environment. The same maneuver will often be imperative in order to sever relationships with bad companions and antisocially motivated gangs. A therapeutically oriented environment will minimize the number of factors that tend to sabotage successful treatment.

Therapy Under Compulsion

There are many situations in which therapy under compulsion constitutes the only avenue through which treatment can be offered to the delinquent. There is a face-saving quality to submission to therapy when the delinquent is threatened by what is for him the highest authority. Long experience with delinquents has convinced us that compulsory measures are often both imperative and desirable for the many youngsters whose judgment is still operable to the extent that specific controls and punitive threats from a legally constituted representative of society can be contemplated and evaluated realistically. This situation prevails too for those whose distrust and hostile resistiveness may obviate any therapeutic attempt whatsoever without the element of compulsion, and for whom the new kind of relationship may actually become rewarding and gratifying once it has been tasted and tested. Only in this way may one be presented with a real opportunity to offer the child a new ego ideal, the loan of ego strength, the identity, and the controls that he basically craves in spite of his loudly proclaimed and confused denials and protestations, as well as apparent provocation of punishment.

Significance of Age and Sex

Age and sex are significant factors when one thinks of juvenile delinquency. While one observes delinquent behavior at all age levels,

there is a tremendous increase in incidence at puberty and during adolescence. Sociologic, cultural, biologic and psychologic factors combine at that time to account for much of the "teen-ager scourge" about which one reads so much today.

Permissive parents, anxious and ready to anticipate and to gratify the instinctual needs of their children, as well as inconsistent and insufficient control and stimulation, have done their part to contribute to permanent ego defects. The biologic sexual changes, the greatly increased instinctual tension, and the factor of mere physical growth in size and strength are additional contributing factors. The need to prove one's masculinity or femininity, to acquire importance, prestige and the material concomitants of status, and to deny the normal bisexual and passive regressive phenomena of this developmental period is part of some of the individual psychodynamic problems that are encountered. Indeed, one might add that the underlying homosexual conflict that is present in almost all adolescents is directly or indirectly responsible for a high percentage of their delinquent manifestations.

Our studies and those of others have revealed important differences in the expression of delinquency in the male and female. The girl acts out in a much more limited area and in fewer ways. Generally she engages in sexual misbehavior. Kleptomania, disorderly conduct in public, or running away from home is occasionally seen, but sexual delinquency is her most typical manifestation of antisocial behavior. The boy, on the other hand, usually exhibits aggressive, destructive activity against property or persons, steals cars, gets drunk, gambles, takes dope, or becomes a con man. He acts out in a much greater variety of ways.

There are many psychodynamic reasons for these differences in the boy and girl so far as antisocial acting-out behavior is concerned. It is not within the scope of this paper to detail most of these reasons. It may suffice to say that adolescence is a crucial and critical development period that constitutes the child's last opportunity to fortify himself for the demands and responsibilities of adulthood. The child who has lived for 13 or 14 years with his body image of smallness, inadequacy and weakness, associated with long-standing dependent needs and passive wishes, is poorly equipped to deal with this new crisis. The outcome of the struggle will depend a great deal on what has transpired during the preceding developmental periods. Usually he will attempt to reinforce the old, inadequate defenses in order to strengthen his newly threatened, tottering character structure, thereby producing further regression and apparent safety from the conflicts that represent a recapitulation of the oedipal period. Old, infantile, partially resolved problems are reopened with even greater intensification, covering and at times almost completely concealing the current issues of the period of adolescence. Exacerbated castration anxiety becomes an added burden to the ever-present separation anxiety.

Regression, with its implicit retreat to safer ground which was more or less acceptable and almost egosyntonic at earlier age levels, now tends to evoke shame to a degree that face-saving of every possible type becomes an all-essential need. Available devices to protest one's masculinity or femininity and to overcompensate for and deny the terror, the helpless dependent feelings, and the urge to seek and to demand the coveted baby state of protectedness include, among others, antisocial acting-out of the variety that is culturally recognized as "rough and tough" delinquent behavior. It is this type of delinquency that one usually encounters during adolescence, particularly in one's private practice.

When oral fixations and regressions with their accompanying hostile envies and greed are so intense that the child is almost constantly aware of an all-pervading wish to receive and to get, these exacerbated feelings during adolescence lead to strong feelings of being feminine or babyish, qualities usually interpreted as shameful "homosexual" ones.

The psychiatric treatment at this time, to which we usually refer as "relationship therapy," involves the establishment of a child-adult relationship in which the therapist becomes a respected and admired dependable figure in the child's life, obviously quite different from the parents, and prepared at all

times to offer large loans of control and strength to the child in whom one recognizes a direct or implied reaching-out for these commodities. The therapeutic road is almost always a long and rocky one, and, as I have already implied, there are few things as uncertain as the therapeutic life of the child who is delinquent.

Comment

One must bear in mind that Redl's now-famous "children who hate" were born into an environment of have-nots who are part of a small corrupt world within the larger one of more or less delinquent double-talking nations whose spokesmen often appear to be masters of denial, displacement, distortion and projection. The true delinquent is indoctrinated very early in the use of these ego-defense mechanisms by parents and peers who are usually blaming everyone but themselves for their difficulties, lacks and acts. These are factors that complicate our approach to the eradication of delinquency, an increasingly widespread phenomenon in our society. They clearly indicate the tremendous importance of prevention as our chief hope. Since we cannot expect to discover a vaccine against mental illness, we must depend on a slow kind of immunization that can be achieved only through the eventual attainment of maturity by a world that is still too full of greed, envy and hostility. The psychiatrist alone is helpless in trying to achieve this goal. He can treat a few of the more willing children and several others under compulsion, but the great majority will be left free to infect other suggestible youngsters and to spread the doctrines of delinquent groups. We shall require more psychiatrists as well as more social workers, psychologists, clergy, sociologists, anthropologists, adjustment teachers, and even more police.

Ultimately we may have more "good" parents, better homes, finer living conditions and excellent schools. With these Utopian achievements, we shall still be forced to continue to expect some forms of antisocial acting-out behavior in the adolescent whose normal and implicit development demands rebellious and defiant assertions of his claim to a place in the adult world. Pearson, in his most recent book concerning the conflict of generations, furnishes us with evidence that the adult is guilty of unconsciously contributing to the acting-out solution of the child, among other things.

Because I have been limited to a brief presentation of a modern-day perspective of the broad field of juvenile delinquency, I am unable to include detailed illustrative case material. The interested reader will find in the accompanying references many varieties of such case studies.

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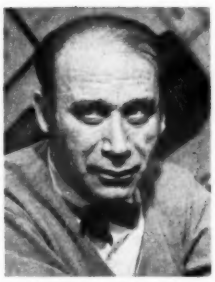
Recent Advances in Neurochemistry

HEINRICH WAELSCH*

Columbia University College of Physicians and Surgeons, New York

The future of neurochemistry rests on furthering our understanding of fundamental biochemical processes as they are integrated into the complex structure of the nervous system. Practical application of this knowledge will be sound and successful as long as it is built on reliable, reproducible experimentation. Hardly any field of organ biochemistry offers the young and the mature biochemist so many exciting, unexplored aspects of research as does the biochemistry of the nervous system under physiologic and pathologic conditions.



HEINRICH WAELSCH

THE last 15 years have seen a rapid development of neurochemistry and a growing awareness on the part of neurologists, psychiatrists, pharmacologists and physiologists of the contributions which the knowledge of the biochemistry of the nervous system may make to our understanding of its function in health and disease. An indication of this increased interest in neurochemistry is the rising number of international and national meetings and symposia on the subject.

Many factors account for the change in attitude and the intensified preoccupation with biochemistry of the nervous system. For many years the biochemical approach to the central nervous system was essentially analytic, the main concern being the chemistry of the lipid constituents of the brain which not only comprise over 50 per cent of its dry weight but increase to this value so conspicuously during the process of myelination. While the analytic approach acquainted us with the substrates of metabolism, it did not tell us anything about the dynamic aspects of metabolism or about its relation to structure beyond the facts unearthed by the classic methods of histology and cytology. Only after the general outlines of intermediary metabolism had been established was the attention of biochemists directed toward its relation to structure and function in specialized organs.

During the period of intensive investigation of the dynamics of intermediary metabolism, which was carried out by studies of isolated

*Professor of Biochemistry, Columbia University College of Physicians and Surgeons; Chief, Psychiatric Research, New York State Psychiatric Institute, New York, New York.

TABLE 1

CEREBRAL BLOOD FLOW AND RESPIRATORY RATE IN MAN[1]

CONDITION OF SUBJECTS	BLOOD FLOW (MILLILITERS PER 100 GM. OF TISSUE PER MINUTE)	RESPIRATION (MILLILITERS O_2 PER 100 GM. OF TISSUE PER MINUTE)
Normal resting	54	3.3
Hyperventilation	34	3.7
Breathing 5 to 7 per cent CO_2	93	3.5
Breathing 85 to 100 per cent O_2	45	3.2
Breathing 10 per cent O_2	73	3.3
Insulin hypoglycemia	61	2.6
Insulin coma	63	1.9
Thiopental anesthesia	52	1.9
Thiopental anesthesia	61	2.1
Schizophrenia	54	3.3
Age 50 to 92 years		
No cerebral disturbance	43	2.4
Senile psychosis	33-39	2.0-2.7

tissue preparations from various organs (tissue slices, homogenates and purified enzymes) and then supplemented by investigations of the fate of isotopically labeled body constituents in vivo, valuable information on the metabolism of the central nervous system was supplied as regards such general metabolic pathways as glycolysis, respiration and amino acid metabolism. It was found that nervous tissue has the enzymatic and metabolic potentialities of any other tissue and that there are only a few metabolic pathways or constituents solely characteristic of it. As in any other organ, the peculiarities of function are the result of a metabolism occurring in a particular structure, and only the knowledge of the chemoarchitectonics of the organ will enable us to understand its function. In no other organ is such knowledge so pertinent, since the central nervous system is characterized by a complexity of structure hardly achieved by any other organ, and the functional units (the neurons) comprise only a fraction of the tissue mass. Here the modern tools for visualization of tissue and cell elements, such as electron microscopy and x-ray diffraction, have forcefully demonstrated the necessity for interpreting metabolism in terms of structure and have given insight—probably sometimes preliminary—as to particular structures as carriers of particular metabolic events. The consideration of structure, furthermore, impressed on the biochemist the necessary caution in applying indiscriminately to the study of the nervous system in health and disease the biochemical methods so successfully applied in internal medicine to the interpretation of the function of organs such as the liver, in which the expression of function is essentially biochemical in nature in contrast to the nervous system.

An impressive demonstration of the protection of the brain from sudden environmental changes is provided by the constancy of cerebral oxygen and glucose consumption under a variety of conditions (table 1). By variations of blood flow, the human adult brain maintains, at high carbon dioxide or oxygen pressure of the inspired air, the oxygen and glucose utilization at about 3.4 ml. and 5 mg. per 100 gm. of tissue per minute, respectively. While the cerebral oxygen utilization and blood flow are considerably higher in children, these values decrease slowly with increasing age. Anesthesia, alcohol intoxication or insulin coma lowers the oxygen utilization. In anxiety states, an increase has not been established unequivocally. In schizophrenia, normal values are found. Lowered values observed in senile psychosis are probably caused by the degree of cerebral atrophy rather than by the mental derangement. It cannot be excluded that local changes of cerebral oxygen and glucose utilization occur in various physi-

ological and pathologic conditions, but there are at present no definitive methods available for such measurements.

A respiratory quotient of close to unity and the equivalence of cerebral oxygen and glucose consumption establish the latter as the main, if not the only, fuel of the brain, the combustion of which supplies the energy for maintenance of structure and function.[2] Although the brain as a tissue has the whole armament of enzymatic activities for the metabolism of a variety of body constituents, the fact that glucose is the main nutrient derived from the circulating blood shows that the special preference for the monosaccharide is due to a mechanism which favors selectively its entrance into the brain. This mechanism, the blood-brain barrier, is of major significance for the protection of the brain from metabolic influences of the body.[3] While the barrier does not affect the rate of gas exchange, it slows down the rate of entrance of most nonlipid soluble substances from the blood, in some cases down to values which make it impossible to detect a net uptake by the brain of some substances such as glutamic acid or other amino acids.

The blood-brain barrier is not only of considerable theoretical interest but also of practical interest, since it governs the exchange of nutrients between brain and blood. Certain structures of the brain appear to have a lowered barrier, for example, the pineal gland, the choroid plexus and the area postrema. Neither the location nor the biochemical mechanism underlying the blood-brain barrier is understood today, but its intensive study under physiologic and pathologic conditions undoubtedly represents one of the most rewarding research projects of the future.

The breakdown of glucose in the brain follows the glycolytic pathway to pyruvic acid and lactic acid, the direct oxidation being only of minor significance. While 10 to 15 per cent of glucose is degraded to lactic acid only, the other 85 to 90 per cent is metabolized as pyruvic acid to carbon dioxide and water through the tricarboxylic acid cycle. A fraction of the carbon of pyruvic acid, as yet not determined exactly, finds its way into the carbon skeleton of the nonessential amino acids and lipid constituents and serves to rejuvenate these constituents of the nervous system. The brain contains the full supplement of enzymes of the glycolytic pathway and the tricarboxylic acid cycle, a large part of the former being found after the fractionation of brain homogenates in the soluble protein fraction of the cell, while the enzymes of the citric acid (tricarboxylic acid) cycle are found in the particulate mitochondria. In brain tissue, as in other tissues, the mitochondria represent the powerhouse in which the energy liberated in the oxidation of pyruvic acid is converted into adenosinetriphosphate, which is drawn on for the requirements of function and maintenance of structure.

Mitochondria, as the seat of oxidative phosphorylation, have been the subject of intensive study to ascertain whether or not the action of some drugs, such as barbiturates or phenothiazines, might be explained by their uncoupling effect which would lower the yield of available energy as adenosinetriphosphate in glucose oxidation. Although in some instances uncoupling of oxidative phosphorylation has been found in vitro, and in others such action of drugs is equivocal, the situation in vivo has not been clarified. It has been shown that the respiration of brain cortex slices either electrically stimulated[4] or in a high-potassium medium[5] is considerably more sensitive to smaller concentrations of drugs, and it has been suggested that the metabolism of slices under these conditions resembles that of the functionally active tissue.

At present, attempts to find any abnormality of carbohydrate metabolism in mental disease have not led to definitive results, although claims of abnormalities in pyruvic acid metabolism or insulin resistance in schizophrenia have been made repeatedly.[6]

Extensive and technically remarkable attempts have been made to localize in particular the enzymes of the carbohydrate and energy metabolism in the structures of the nervous system either by quantitative cytochemical technics or by isolation and analysis of cells and their parts.[7-9] It could be shown that the various cells investigated, as well as their

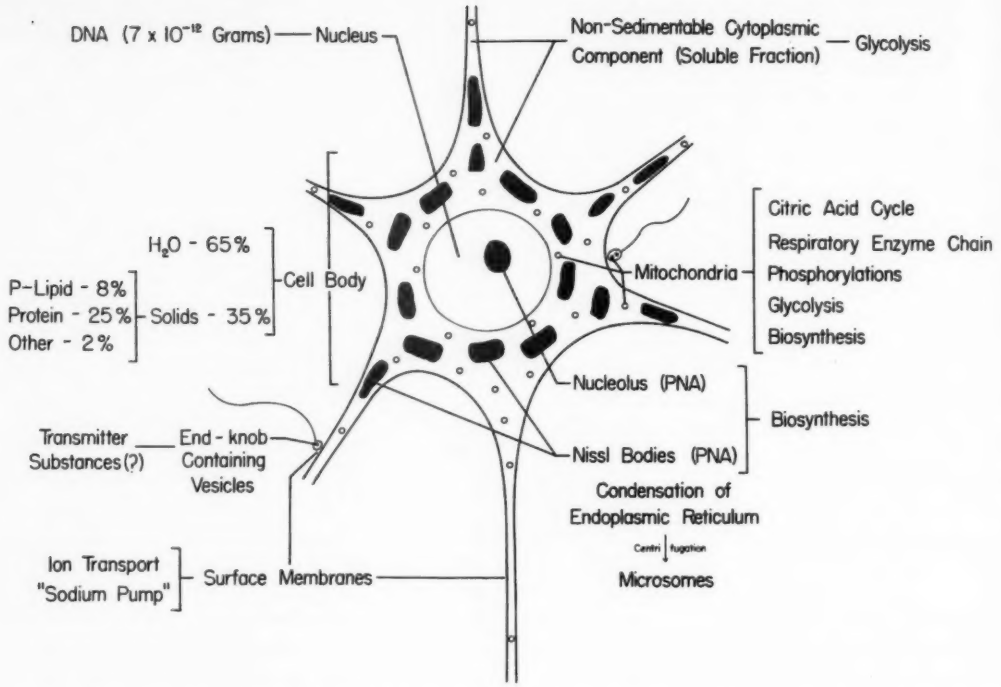


FIGURE 1. Schematic representation of the cell body and processes of a typical motor neuron, showing probable distributions of biochemical components in relation to cytologic details. The large, centrally placed nucleus, its contained nucleolus, the Nissl bodies in the perikaryon (excluding the axon hillock) and the proximal portions of the dendrites are depicted as they would appear in a Nissal preparation. Superimposed on this is an indication of the characteristic distribution of mitochondria. Also included are the proximal portion of the axon (*bottom of figure*) and two boutons terminaux forming an axomatic and an axodendritic synapse. The axon and end-knobs are shown as they would appear histologically as the result of silver impregnation.

Acknowledgment: For this schematic representation I am highly indebted to Dr. Alfred Pope of Harvard University. It represents a modification of a previous picture (Pope, A.: In Richter, D. [ED.]: The Metabolism of the Nervous System. London, Pergamon Press, Inc., 1957).

parts, are characterized by specific concentrations of the enzymes of glucose metabolism, concentrations which vary within narrow limits. It could further be shown that the enzyme concentrations as measured in vitro are far in excess of those necessary for the metabolism in vivo, a fact which probably is a reflection of the low substrate and cofactor concentrations which make high enzyme concentrations mandatory for rapid metabolism. A schematic representation of the distribution in neurons of major metabolic pathways is given in figure 1.

With the exception of a few significant contributions, the biochemistry of the nitrogenous constituents of the nervous system has been under intensive study only recently. But since this group of compounds comprises proteins, amino acids and amines, substances which may be of considerable functional significance, they are attracting rapidly increasing attention. The pool of free amino acids in the central nervous system serves a number of functions, some peculiar to this organ.[10] From this pool are drawn the amino acids used as building stones for the proteins, and to it are returned the amino acids liberated in their breakdown. Secondly, the amino acids in the pool may serve in emergency situations as substrates of respiration and thereby supply energy. Thirdly, they are the mother substance of a number of amines, such as serotonin,

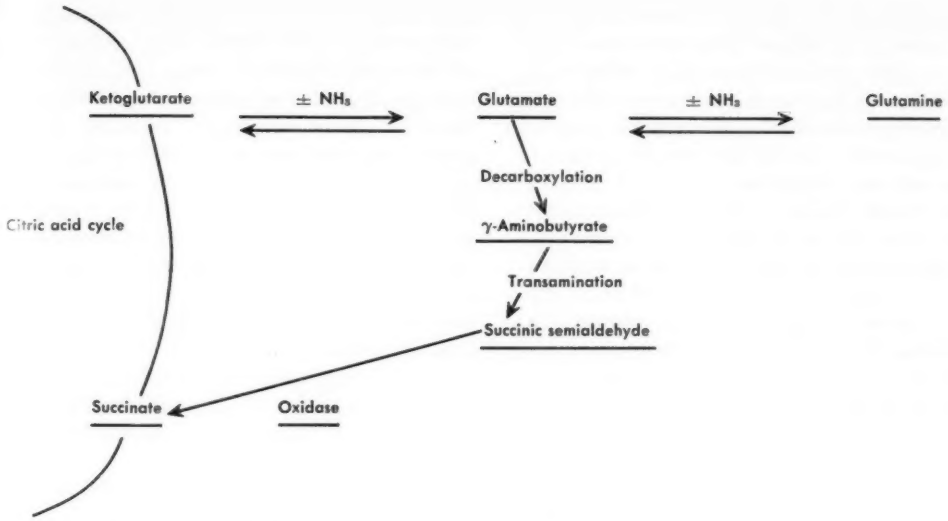


FIGURE 2. The metabolism of glutamic acid in the central nervous system.

norepinephrine and epinephrine. Finally, dicarboxylic acids, such as glutamic acid, may be involved in the maintenance and transport of cations and thereby in the partial compensation of the anionic deposit in the nervous system.

In the mammalian brain the pool of free amino acids is characterized by a concentration of glutamic acid higher than that encountered in any other organ (150 to 180 mg. per 100 gm. of tissue), and the nitrogen of this dicarboxylic amino acid together with its metabolic derivatives glutamine, glutathione and γ-aminobutyric acid comprises close to two-thirds of the total α-amino nitrogen of the nonprotein fraction of the brain. In this fraction there are present in high concentrations acetyl aspartic acid, γ-aminobutyric acid and cystathionine, compounds occurring in brain only—and cystathionine[11] specifically in Primate brain. While nothing is known at present about the significance of the occurrence of acetyl aspartic acid and cystathionine, great attention has been paid during recent years to the metabolism and functional significance of γ-aminobutyric acid.[12] This amino acid is derived from glutamic acid by decarboxylation, and its carbon skeleton is converted to succinic acid after deamination and oxidation. Since in other tissues glutamic acid is deaminated to ketoglutaric acid which is decarboxylated to succinic acid, the γ-aminobutyric acid pathway provides an alternate pathway for the metabolism of glutamic acid in the brain (figure 2). This is possible because of the unique occurrence of a pyridoxal phosphate-dependent glutamic acid decarboxylase in brain and not in other tissues.[13] Later it was found that γ-aminobutyric acid is the substance occurring in brain extracts that is responsible for the inhibition of the stretch receptor reflex in crayfish,[12,14] and its effect on the mammalian cortex has been related to an inhibition of the excitatory axodendritic synapse.[12,15]

Besides being the mother substance of γ-aminobutyric acid, glutamic acid takes part in a number of metabolic reactions of probable functional significance. The pathways ketoglutaric acid + NH_3 → glutamic acid and glutamic acid + NH_3 → glutamine represent the two mechanisms for the removal of ammonia, mechanisms which are supported by the presence of high activity of the corresponding enzymes in brain. Ammonia has been assumed for many years to be toxic to the nervous system. It is interesting to note that

glutamic acid as well as γ-aminobutyric acid is unable to penetrate the intact blood-brain barrier, and they are therefore not taken up by the intact brain from the circulating blood in measurable amounts. In contrast the amide of glutamic acid (glutamine) can be shown to penetrate the blood-brain barrier.[16]

A possible close relationship between glutamic acid and its metabolic derivatives and the function of the nervous system has been under consideration since the effect of glutamic acid on petit mal seizures and the performance of mentally defective persons was studied.[16] Clinical results were too erratic and slight to be of therapeutic value, but they did focus attention on the role of glutamic acid in the normal and aberrant functioning of the central nervous system. Added support for such a relationship was drawn by the development of antimetabolites (methionine sulfoxide, methionine sulfoximine)[17,18] which blocked the conversion of glutamic acid to glutamine and were able to precipitate seizures in animals. Surgically obtained human epileptogenic foci also appeared to show a deficiency of glutamine, a finding which led to the administration of glutamine and asparagine to epileptics with results akin to those obtained with glutamic acid.[18] In cats with paroxysmal epileptogenic electric activity in cortical lesions produced by freezing of a small area, a significant drop in the concentrations of glutamic acid, glutamine and glutathione was found while the γ-aminobutyric acid concentration remained constant.[19] While this finding may be explained by assuming that the metabolism of the cortex is geared to the maintenance of the γ-aminobutyric acid level, it may on the other hand suggest that the γ-aminobutyric acid involved in the normalization of the seizure activity represents a small fraction only of that present in the tissue. This line of investigation shows the overlap of biochemical and physiologic problems characteristic of the recent approach to neurochemical problems.

It had been assumed for some time that the proteins of the central nervous system do not turn over and, once deposited, are not metabolized, just as the adult neuron does not duplicate. More recently it has been shown, first with optical methods and later with the aid of isotopically labeled amino acids, that the proteins of the brain have a considerable turnover.[10,20] As in all organs, there are in the central nervous system proteins with a wide variety of turnover rates, some being metabolized and replaced at a rapid rate and some at a slow rate. The rapidly metabolized protein fractions of the brain have a turnover not much slower than the corresponding fractions of liver protein. Considerable speculation has been going on for some time as to whether or not nucleic acids or proteins of the brain as macromolecules are the organic basis for the storage of information, i.e., memory. At present these speculations have not matured to a sufficient degree to offer the design of a definitive experimental approach.

Recently, attempts have been made to find a metabolic error in the composition of the blood proteins in schizophrenia. It was first claimed that owing to the increased concentration of a copper-containing protein (ceruloplasmin), the rate of oxidation of certain organic compounds or of epinephrine, or both, is increased in the serum of these patients. It was further claimed that a specific serum protein fraction from schizophrenic patients, when injected into nonschizophrenic subjects, would produce psychotic episodes. Although it cannot be ruled out that the rationale behind these approaches is sound, none have given persuasive evidence and many of the results cannot be accepted on methodologic grounds.

While, as pointed out, the proteins of the brain itself are degraded and resynthesized at a rate comparable to those in other organs, the question arises how the proteins of the axoplasm, sometimes considerably distant from the neuronal cell body, are synthesized. From constriction experiments and work with isotopes the possibility is suggested that these proteins are not synthesized locally in the axon but are flowing down the axon from the cell body of the neuron where they are synthesized.[20]

Much progress has been made concerning the metabolic distribution of effector substances of neurohormonal nature, although their significance in the mechanism of nerve

function is still unknown. The classic neurohormonal transmitter acetylcholine is synthesized by an enzyme, cholinacetylase, with the participation of adenosinetriphosphate as a source of energy and coenzyme A as an essential compound of the enzymatic system. It is, furthermore, split by a specific cholinesterase occurring in the nervous system. This is not the place to discuss the pros and cons of the various roles assigned to acetylcholine in the function of the nerve,[21] but the accumulated evidence supports the original concept of Loewi and Dale that acetylcholine acts as a synaptic transmitter in cholinergic nerves. In adrenergic nerves, norepinephrine has been recognized as the prevalent transmitter substance.[22] The central nervous system and other organs such as the adrenals contain the enzymes which catalyze the decarboxylation of dihydroxyphenylalanine to norepinephrine, which in the adrenals would then be methylated to epinephrine.

The most recent member of the group of supposed effector substances, serotonin, has attracted considerable attention of late because of various hypotheses assigning to this amine an essential role in the etiology of mental disease. Although serotonin itself cannot penetrate the blood-brain barrier, its precursor 5-hydroxytryptophan is able to do so and is then decarboxylated in the brain to serotonin.[23] In the search for a function of this amine, extensive use of inhibitors of amine oxidase has been made, the enzymes of which inactivate serotonin by oxidative deamination. The antagonism of serotonin and lysergic acid diethylamide in pharmacologic preparations has led to the supposition of either a deficiency or an overproduction of serotonin in the brains of schizophrenic persons.[24] While this suggestion represents an attractive hypothesis, there is no direct experimental evidence to support it.

The chemical similarity between mescaline and epinephrine is responsible for attempts to implicate the metabolic products of epinephrine, particularly adrenochrom, in the etiology of schizophrenia. Although sympathomimetic amines might be involved in the etiology of mental disease, the experiments and conclusions based on the adrenochrom hypothesis have come under justifiable criticism, particularly in their methodologic aspects. Therefore, at present none of these attempts have led to any useful or reproducible lead as to the etiology of schizophrenia.[6]

The chemistry of the lipids, for many years the main concern of biochemists interested in the chemistry of the nervous system, has become more and more the object of organic chemical studies. The interest is now centering on the characterization of the high molecular substances such as the gangliosides which contain a variety of monosaccharides, hexuronic acid and hexosamine. The study of the brain lipids has led to the discovery of a highly labile compound, neuraminic acid, a condensation product of hexosamine and pyruvic acid and an essential component of the gangliosides.[25]

Considerable effort has been spent on the enzymatic mechanism of degradation and synthesis of lipids, and the general outlines of their metabolism in the normal nervous system as well as in degeneration have been established.[26] While there is a rapid turnover and synthesis of fatty acids and cholesterol during the period of myelination, these components show only a slow turnover, and probably none at all in the case of cholesterol in the adult animal.[27] This fact may be of significance in the understanding of the destructive processes in demyelinating diseases, as the cells producing myelin appear to lose their synthetic ability in the mature brain. On the other hand, the elucidation in experiments in vitro of the enzymatic synthesis of many phosphatides and the involvement of the pyrimidine nucleotides in these synthetic processes[28] suggest the possibility that a further understanding of the fundamental biochemistry of lipids may lead to tools to reverse the destruction of the myelin components in demyelinating diseases.

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BOOKS RECEIVED

Books received are acknowledged, and, as space permits, those of principal interest to our readers are reviewed more extensively. Reviews appear in this issue starting on page A-171; additional listings are on page A-178.

New Methods of Studying Gaseous Exchange and Pulmonary Function. By Alfred Fleisch, M.D., Professor and Director, Department of Physiology, Université de Lausanné Faculté de Médecine, Lausanne, Switzerland. 116 pages with 33 illustrations. 1960, Charles C Thomas, Springfield, Illinois. $5.75.

Diabetes. By Robert H. Williams, M.D., Executive Officer and Professor of Medicine, University of Washington School of Medicine, Seattle, with 54 contributors. 793 pages with 192 illustrations. 1960, Paul B. Hoeber, Inc., Medical Book Division of Harper & Brothers, New York. $20.00.

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Neurologic Examination of the Infant

Newborn to 12 Months

PAUL M. ELLWOOD, JR.*
Elizabeth Kenny Institute
Minneapolis

SCIENTIFIC EXHIBIT

THE examination technics illustrated in this exhibit represent an attempt to systematize a series of uniquely infantile phenomena into a practical pediatric neurologic examination procedure. Utilizing these and similar methods, the accuracy of the neurologic examination of infants should approach that of the adult neurologic examination.

*Medical Administrator, Elizabeth Kenny Institute; Assistant Medical Director, Sister Elizabeth Kenny Foundation; Assistant Clinical Professor of Pediatrics and Neurology, University of Minnesota Medical School, Minneapolis, Minnesota.

Adapted from an exhibit which received the first award at the 1958 meeting of the American Academy of Neurology in Philadelphia and a certificate of merit at the 1959 scientific session of the American Medical Association in Atlantic City.

Head and Cranial Nerves

Examination of the Head

Transillumination: for detecting cysts, subdural hematomas and severe hydrocephalus

FIGURE 1. A healthy-appearing but slowly developing eight month old infant.

FIGURE 2. In a darkened room, a flashlight is pressed against the skull.

FIGURE 3. The entire skull transilluminates, indicating a diagnosis of hydranencephaly.

Measurement of the occipitofrontal circumference: for detecting hydrocephalus, microcephaly and craniosynostosis

FIGURE 4. Position of tape measure for measuring occipitofrontal circumference.

FIGURE 5. Microcephaly in a one year old infant. Skull circumference is 36 cm.

NORMAL OCCIPITOFRONTAL SKULL MEASUREMENTS

Age	Mean	
	Inches	*Centimeters*
Birth	13.8	35.0
1 month	14.9	37.6
2 months	15.5	39.7
3 months	15.9	40.4
6 months	17.0	43.4
9 months	17.8	45.0
12 months	18.3	46.5
18 months	19.0	48.4
2 years	19.2	49.0

One standard deviation equals 0.5 in. or 1.2 cm.

Examination of the Cranial Nerves

The following normal responses are obtained in testing the cranial nerves of infants.

I. Olfactory. Flare of the alae nasi in response to benzoin tincture from first days of life.

II. Optic. Pursuing a moving object with the eyes begins with stage I in the newborn period and reaches stage III by the age of four months (figure 6). A tape measure serves as a satisfactory test object.

III. Oculomotor, IV. trochlear, VI. abducens. Light reflex: The position of a reflected light is slightly medial to the center of the pupil (figure 7). Doll's eye phenomenon: The newborn's eyes rotate in a direction opposite to that of the passively rotated head.

V. Trigeminal. Corneal reflex is elicited by touching the cornea with a point of cotton, producing closure of the eyes. Rooting response, consisting of mouth opening and head turning toward the stimulus, is obtained by touching the infant's cheek with a nipple or finger.

VII. Facial. Nasolabial folds should be of equal depth during crying. Palsy of the VII nerve on the right side causes a noticeable difference in closure of the eyelids (figure 8).

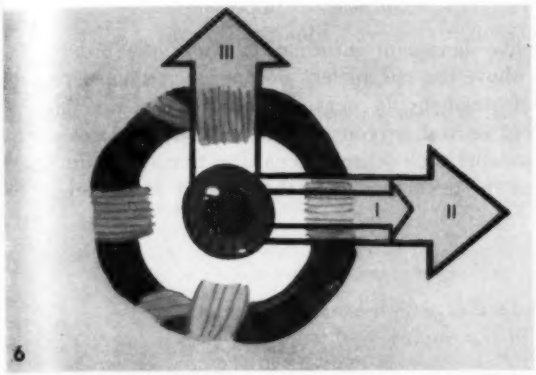
VIII. Acoustic. The newborn blinks in response to a noise (clap or bell). Response in a one month old infant is evidenced by a change in the output of motor activity. By the age of four or five months, the infant attempts to localize the source of the sound by turning his head toward it.

IX. Glossopharyngeal, X. vagus. The infant swallows and has a symmetrically mobile palate and posterior pharyngeal wall.

XI. Accessory. Observations of head support show that the newborn turns his head from the midline when prone (figure 9); the four month old infant lifts his head when prone (figure 10). At eight months, head control is complete (figure 11).

XII. Hypoglossal. Retrusion: The tongue protrudes in the midline when stimulated at its tip (figure 12).

Head and Cranial Nerves



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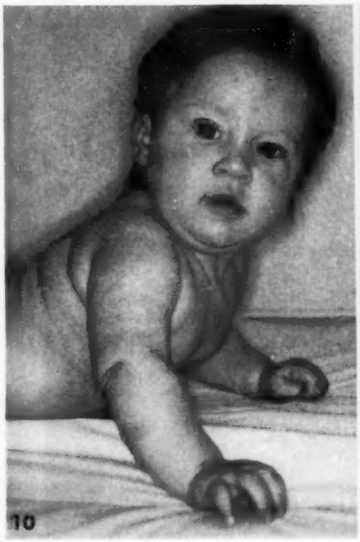
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Development

Examination of Muscle Strength and Coordination

A simplified examination of development yields significant information about the orderly maturation of the cerebral cortex. Most lesions above the red nucleus do not assert themselves during the newborn period. Ideally, each test performed should measure maturation of function at different peripheral sites controlled by different central nervous system areas. The developmental levels of the various extremities should parallel each other in regard to tonus, coordination and reflexes. Most of these activities represent the development of the afferent and efferent systems.

Supine lying

Reflexes acting on the head, neck and trunk as well as output of motor activity are tested with the infant in the supine position.

FIGURE 13. In the newborn, rotation of the head tends to produce flexion of the extremities, especially on the occipital side. Movements of the head are associated with movements of the trunk in the same direction.

FIGURE 14. With head in the midline, the hands of a four month old infant meet on the chest.

FIGURE 15. An eight month old infant rolls over from the supine position.

Pull to sit

Musculature of the neck, shoulder, arm, elbow and upper trunk are tested by pulling the infant to a sitting position.

FIGURE 16. Arms and legs are flexed in the newborn.

FIGURE 17. In the four month old infant, the arms and legs are extended.

FIGURE 18. The eight month old infant gives active assistance in assuming a sitting position.

Hand control

Visual, motor and coordinating activities as well as the musculature of the hand are observed in hand control tests.

FIGURE 19. Clenched hand with grasp reflex in a newborn.

FIGURE 20. Open hand with a less intense grasp reflex in a four month old infant.

FIGURE 21. An eight month old infant picks up a block with all four fingers. Grasp reflex is gone.

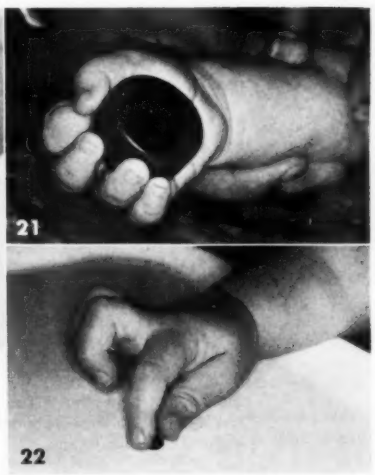

FIGURE 22. A 12 month old infant picks up a pellet with thumb and index finger.

Standing

Muscles acting on the trunk, hips, knees and ankles are tested with the infant in the standing position.

FIGURE 23. Primitive stepping pattern in a newborn.

FIGURE 24. Minimal tonus of lower extremities in a four month old infant.

FIGURE 25. Hyperextension of knees and ankles with fair support of entire body in an eight month old infant.

FIGURE 26. Early walking with pronounced lordosis and lateral rotation of the lower extremities may be seen in infants from 12 to 16 months of age.

Reflexes

Moro reflex

Eliciting the Moro reflex is an excellent maneuver for observing movement in all extremities. It disappears with cortical control.

Deep tendon reflexes

Deep tendon reflexes are present and symmetric at all ages. The Babinski response is present symmetrically up to 18 months.

FIGURE 27. The strongest possible stimulus for obtaining a Moro reflex consists of dropping the child after lifting it by the arms for 3 or 4 in. The triggering mechanism appears to be a sudden tension in the neck extensors.

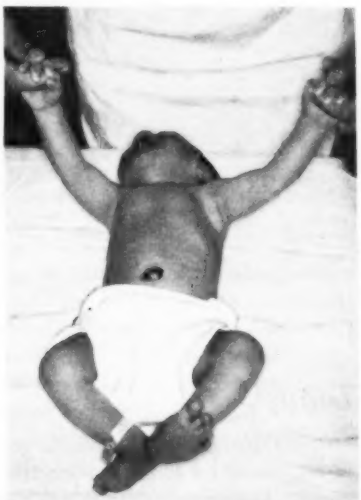

FIGURE 28. Full-blown Moro response in a newborn.

FIGURE 29. In a four month old infant, the Moro reflex is present but involves less of the organism, is more difficult to trigger, and is of shorter duration.

FIGURE 30. The Moro reflex is absent in an eight month old infant.

Trunk and Extremities

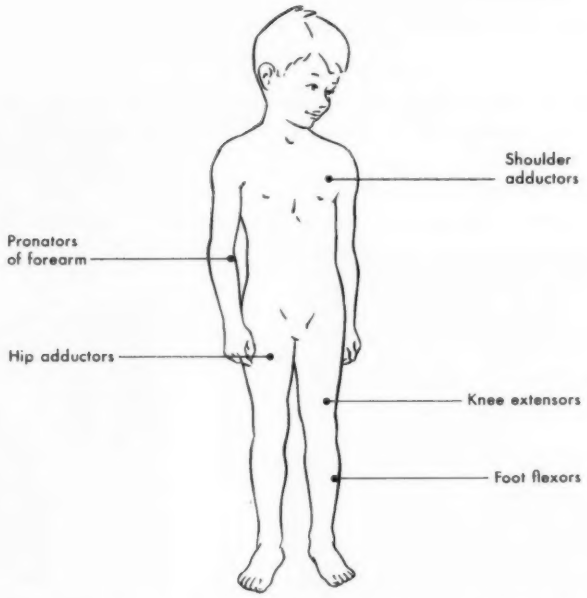

FIGURE 31. The most frequent sites of increased tonus in upper motor neuron disease.

Tonus

Observations of muscle tonus through palpation and passive motion of the extremities often provide the best evidence of lesions in the motor pathways from the cortex to the motor end-plate.

Growth

Upper motor neuron lesions in children commonly produce discrepancies in the size of the extremities. Even the size of the fingernails may be a good sign of a long-standing brain lesion.

Critical Clues

Symmetry of motion, tone and response
Orderly acquisition of motor skills
Regression and progression of reflexes

A 25 minute, 16 mm. sound film on developmental neurology is available for loan to medical groups. Write to Dr. Paul M. Ellwood, Jr., 1800 Chicago Avenue, Minneapolis 4, Minnesota.

Rational Use of Vitamins in the Practice of Medicine

ROBERT S. GOODHART*

The National Vitamin Foundation, New York

ROBERT S. GOODHART

In a published study, the Council on Foods and Nutrition of the American Medical Association[1] stated, "Vitamin preparations are used extensively and are valuable when used properly. For the most intelligent use and beneficial results in preventive or therapeutic medicine, the values and the limitations of vitamins should be realized. It is important that a clear differentiation be made between vitamins as dietary supplements and vitamins as therapeutic agents." I concur with this statement by the Council and, in this article, shall endeavor to set forth a rational basis for the use of vitamins in the practice of medicine.

Basic Considerations

The Food and Nutrition Board of the National Research Council[2] has published a table of recommended dietary allowances designed to maintain good nutrition in healthy persons in the United States under current conditions of living and to cover nearly all variations of requirements for the listed nutrients in the population at large (table 1). These allowances are meant to afford a margin of sufficiency above minimal requirements and are therefore planned to provide a buffer against the added needs of various stresses and to make possible other potential improvements of growth and function. *The allowances are not to be considered adequate either to meet the additional requirements associated with disease or for nutrient repletion in severely depleted persons.*

In any section of the country, considerably more than one-half the population can be expected to fail to meet in full the recommended dietary allowances for one or more nutrients.[3] This does not mean that all such persons are malnourished or vitamin deficient. Nutrient requirements vary widely, not only from person to person but also from time to time in the same person, and, since the recommended dietary allowances are designed to assure good nutrition for the majority of healthy persons, it follows that many people can be well nour-

*Scientific Director, The National Vitamin Foundation, New York, New York.

TABLE 1

RECOMMENDED DAILY DIETARY ALLOWANCES*

(REVISED 1958)

	AGE (YEARS)	WEIGHT (KG.)	WEIGHT (LB.)	HEIGHT (CM.)	HEIGHT (IN.)	CALORIES†	PROTEIN (GM.)	CALCIUM (GM.)	IRON (MG.)	VITAMIN A (I.U.)	THIAMINE (MG.)	RIBOFLAVIN (MG.)	NIACIN‡ (MG. EQUIV.)	ASCORBIC ACID (MG.)	VITAMIN D (I.U.)
Men	25	70	154	175	69	3200	70	0.8	10	5000	1.6	1.8	21	75	
	45	70	154	175	69	3000	70	0.8	10	5000	1.5	1.8	20	75	
	65	70	154	175	69	2,550	70	0.8	10	5000	1.3	1.8	18	75	
Women	25	58	128	163	64	2300	58	0.8	12	5000	1.2	1.5	17	70	
	45	58	128	163	64	2200	58	0.8	12	5000	1.1	1.5	17	70	
	65	58	128	163	64	1800	58	0.8	12	5000	1.0	1.5	17	70	
	Pregnant (second half)					+300	+20	1.5	15	6000	1.3	2.0	+3	100	400
	Lactating (850 ml. daily)					+1000	+40	2.0	15	8000	1.7	2.5	+2	150	400
Infants§	2/12-6/12	6	13	60	24	Kg. x 120	—	0.6	5	1500	0.4	0.5	6	30	400
	7/12-12/12	9	20	70	28	Kg. x 100	4	0.8	7	1500	0.5	0.8	7	30	400
Children	1-3	12	27	87	34	1300	40	1.0	7	2000	0.7	1.0	8	35	400
	4-6	18	40	109	43	1700	50	1.0	8	2500	0.9	1.3	11	50	400
	7-9	27	60	129	51	2100	60	1.0	10	3500	1.1	1.5	14	60	400
	10-12	36	79	144	57	2500	70	1.2	12	4500	1.3	1.8	17	75	400
Boys	13-15	49	108	163	64	3100	85	1.4	15	5000	1.6	2.1	21	90	400
	16-19	63	139	175	69	3600	100	1.4	15	5000	1.8	2.5	25	100	400
Girls	13-15	49	108	160	63	2600	80	1.3	15	5000	1.3	2.0	17	80	400
	16-19	54	120	162	64	2400	75	1.3	15	5000	1.2	1.9	16	80	400

*The allowance levels are intended to cover individual variations among most normal persons as they live in the United States under usual environmental stresses.

†Calorie allowances apply to individuals usually engaged in moderate physical activity. For office workers or others in sedentary occupations, they are excessive. Adjustments must be made for variations in body size, age, physical activity and environmental temperature.

‡Niacin equivalents include dietary sources of the preformed vitamin and the precursor tryptophan; 60 mg. tryptophan equals 1 mg. niacin.

§The Board recognizes that human milk is the natural food for infants and feels that breast feeding is the best and desired procedure for meeting nutrient requirements in the first months of life. No allowances are stated for the first months of life. Breast feeding is particularly indicated during the first month when infants show handicaps in homeostasis due to different rates of maturation of digestive, excretory and endocrine functions. Recommendations as listed pertain to nutrient intake as afforded by cow's milk formulas and supplementary foods given the infant when breast feeding is terminated. Allowances are not given for protein during infancy.

ished on diets that do not meet the allowances in one or more respects. What does not follow is the frequently drawn conclusion that the table of recommended dietary allowances is not the proper yardstick to apply in developing preventive nutrition programs for population groups or individuals. For such a conclusion to be justifiable, it would have to be shown that nutrients are distributed among the population and consumed according to need, a phenomenon that never has and probably never will occur in this or any other country. In this same connection, it is true that some persons deny the proposition of the Food and Nutrition Board[2] that it is desirable "to provide a buffer against the added needs of various stresses and to make possible other potential improvements of growth and function." Here, it seems to me, there is the implied assumption that the sciences of medicine and nutrition have advanced to the stage where the precise nutrient requirements of individuals readily can be determined, a goal which we are far from attaining.

In order to safeguard the nutritional welfare of a substantial minority, it is essential that a dietary standard be applied which will provide a liberal margin of safety for the majority. In order to protect the nutritional status of the individual patient, the prudent physician will assume until he can prove otherwise that his patient belongs to that sizable minority having greater-than-average nutritional requirements. *The recommended dietary allowances of the Food and Nutrition Board represent the best available standards for both public health purposes and the prophylactic nutritional management of the individual healthy patient.*

Severe, acute vitamin deficiency diseases caused by poor diets alone are no longer common in this country. In fact, except for infantile scurvy, which may be on the increase in some areas of this country and Canada, such diseases are medical curiosities when they do occur. Severe deficiency states secondary to or precipitated by other metabolic disorders, diseases, alcoholism and iatrogenic causes are relatively common, however. Low-grade, long-term undernutrition, which may be diagnosed only by inference from the dietary and medical histories, a variety of gastrointestinal and neurasthenic-type complaints often associated with anemia and, in children, with growth failure and response to therapy, is the form of nutritional deficiency of dietary origin with which the physician is most frequently confronted. Here is where his diagnostic acumen and skills and his patience are put to the test. Unfortunately, here also is where the results of nutritional therapy frequently are very difficult to evaluate; nevertheless, when the diagnostic workup fails to reveal other sufficient cause for the symptomatology, the patient should receive the benefit of adequate nutritional therapy before he is labeled a psychoneurotic or hypochondriac. Some possible causes of vitamin deficiency states are given in table 2.

TABLE 2

CAUSES OF VITAMIN DEFICIENCY STATES

SOCIOECONOMIC CAUSES	
Living conditions	Income
Working conditions	Education
Available foods	Cultural patterns and faddism
OTHER CAUSES OF DIMINISHED NUTRIENT INTAKE	
Anorexia	Neuropsychiatric disorders
Allergies	Edentia
Therapeutic diets	Pregnancy
Gastrointestinal disorders	
CAUSES OF INCREASED NUTRIENT REQUIREMENT	
Physical exertion	Pregnancy and lactation
Environmental extremes	Rapid growth
Fever	Certain toxic agents
Hyperthyroidism	Certain therapeutic regimens
INTERFERENCE WITH ABSORPTION	
Hypermotility of intestinal tract or reduction in absorbing surface	Achlorhydria or achylia gastrica
Biliary disease	Vitamin deficiency
Laxative or purgative therapy	Gastrointestinal surgery
INTERFERENCE WITH UTILIZATION OR STORAGE	
Liver disease	Malignancy
Diabetes mellitus	Antibiotic therapy
Hypothyroidism	Vitamin deficiency
CAUSES OF INCREASED LOSS OR EXCRETION	
Polyuria	Lactation
Blood loss	Negative nitrogen balance

The dietary vitamin inadequacies most fre-

quently reported on diet surveys in the United States are those of vitamin A, vitamin C, thiamine and riboflavin. A major reason for this is that in the American diet a certain few foods are depended on as major sources of these vitamins. These are foods which, for one reason or another, are not eaten in sufficient quantities by many people, e.g., deep green leafy and yellow vegetables for carotene (provitamin A); tomatoes and citrus fruits for vitamin C; pork, enriched flour, bread and fortified cereals for thiamine; and milk for riboflavin.

If Vilter[4] is right in his statement that the average adequate diet contains from 1 to 2 mg. of vitamin B_6 per day and if Harding, Plough and Friedemann[5] are correct in their estimate that the minimal daily requirements of healthy young male adults range from 1.93 to 2.76 mg. per day, then vitamin B_6 deficiency may prove to be the most common vitamin deficiency in this country. Evidence is accumulating that relative vitamin B_6 inadequacy may occur frequently in certain conditions of stress, such as pregnancy and a variety of disease states; however, as yet, data on hand are insufficient to justify an estimate of the incidence of inadequacy of dietary vitamin B_6 in the general population.

Vitamins A, D, E and B_{12}, once absorbed, are well stored within the body. It may take from one year (for vitamin A) to as long as seven years (for vitamin B_{12}) of practically complete deprivation of one of these vitamins for a previously well-nourished healthy adult to show evidences of vitamin deficiency. Thus, a daily supply of these vitamins from external sources is not essential, and deficiencies of them rarely are a critical matter in the management of non-nutritional intercurrent diseases, except in infants and small children who have not had an opportunity to build up large reserves within the liver and other tissues, in malnourished individuals, and probably in some persons with liver disease, where there may be failure to store or release the vitamin in the normal fashion. Nevertheless, it is recommended that the daily requirements for these vitamins be met if it is at all feasible. There is nothing to be gained by permitting the body stores to become depleted.

Normally, the major source of biotin and vitamin K appears to be the flora of the intestinal tract. Thus, the possibility of deficiency of these vitamins in children and adults must be borne in mind when for some reason the intestinal flora is abnormal or depleted. Such a condition may be found in the newborn, or as a result of prolonged therapy with intestinal antibiotics, in situations in which absorption of fats and fat-soluble vitamins (vitamin K) is impaired, and in the occasional faddist who consumes large amounts of raw egg white (biotin).

Although inositol and choline can be synthesized within the body, an additional supply from the diet appears to be desirable and perhaps essential; however, the amounts of choline and inositol in the American diet appear to be ample. Primary dietary deficiencies have not been described.

In the presence of adequate amounts of other B vitamins, niacin can be synthesized within the body from tryptophan; about 60 mg. of dietary tryptophan is equivalent to 1 mg. of niacin. In a healthy person on a liberal intake of high-quality protein, it is doubtful that the dietary content of preformed niacin needs to be considered; however, since tryptophan is used preferentially by the body for tissue building, it is important that adequate amounts of preformed niacin be supplied in any situation in which the intake of protein is little more than adequate to meet tissue requirements for growth, maintenance and repair. Tryptophan is not an economical source of niacin.

The fat-soluble vitamins are vitamins A, D, E and K. Vitamin K, which is essential for the synthesis of prothrombin, is not as well stored within the body as are the other fat-soluble vitamins. During prolonged antibiotic therapy, vitamin K deficiency (caused by the suppression of vitamin K-producing bacteria) may be responsible for some of the bleeding that occurs. Severe diarrhea may result in lowered plasma prothrombin levels, and when bile is excluded from the intestine, as in obstructive jaundice, the absorption of vitamin K may be seriously impaired and clinical signs may develop.

The bile salts are necessary for the absorption of natural vitamin K (vitamin K_1) and for the absorption of the other fat-soluble vitamins. The absorption of fats promotes the absorption of these vitamins; deficiencies may develop with steatorrhea. Preformed vitamin A is not as dependent on the absorption of fat as is carotene, and it is less susceptible to destruction in the intestine; therefore, vitamin A is preferred to its precursor in the presence of gastrointestinal disease with malabsorption.

Water-miscible or water-soluble or both forms of all the fat-soluble vitamins, as well as preparations suitable for parenteral administration, are commercially available. Menadione and the water-soluble analogs of vitamin K appear to be as effective as vitamin K_1 in the treatment of hemorrhagic disease of the newborn and in the preoperative preparation of patients; however, given intravenously, vitamin K_1 reliably and rapidly decreases the prolonged prothrombin time produced by administration of DICUMAROL®, an effect not seen with the synthetic vitamin K analogs.

With two exceptions, the water-soluble vitamins (the so-called B vitamins and vitamin C) are much more dependent for physiologically adequate tissue content on recent and current dietary intake and are considerably less well stored within the body than are vitamins A, D and E. The two exceptions are vitamin B_{12}, which is well stored in the healthy liver, and biotin, which is supplied to the body through synthesis by the intestinal flora.

In addition to vitamin C (ascorbic acid), vitamin B_{12} and biotin, the water-soluble vitamins include thiamine, riboflavin, niacin, vitamin B_6, pantothenic acid and folic acid. Choline and inositol also frequently are included in this group.

The recommended dietary allowances have been promulgated by the National Research Council only for vitamin A, thiamine, riboflavin, niacin, vitamin C and vitamin D. The estimated daily amounts required by healthy adults of other vitamins are given in table 3.

TABLE 3

ESTIMATED DAILY AMOUNTS OF CERTAIN VITAMINS REQUIRED BY HEALTHY ADULTS

VITAMIN	DAILY AMOUNT
Vitamin B_6	About 2 mg.
Pantothenic acid	7-10 mg.
Folic acid	0.5-1 mg.
Vitamin B_{12}	About 2 μg.
Biotin (synthesized in the intestine)	150-300 μg.
Vitamin E (varies directly with amount of polyunsaturated fat in the diet)	5-30 mg.
Vitamin K (synthesized in the intestine)	About 1 mg.
Choline	Perhaps 150-250 mg.
Inositol	1 gm. in ordinary diet

Supplemental Vitamin Therapy

Supplemental vitamin therapy means the practice of supplementing the usual diet of presumably healthy persons with pharmaceutical vitamin preparations. The principle involved here is the same as that behind the enrichment and fortification of foodstuffs with vitamins. The Food and Nutrition Board of the National Research Council and other public health authorities, recognizing the prevalence of certain dietary inadequacies due to customary practices in the manufacture or processing of staple foods and recognizing the magnitude of the task of changing such practices or the food habits of the consumer, actively support the enrichment of white flour, rice, corn and other cereal grains and the fortification of margarine with vitamin A to prevent the development of vitamin deficiency states and to improve the general nutrition.

Unfortunately, the enrichment of cereal grains is by no means universal in the United States; if it were, it obviously could make an important contribution to the health of only those people who eat substantial quantities of such foods. This includes the lowest economic groups, most children, many persons engaged in hard physical work, and elderly persons. The more or less sedentary urban adult, who can afford other foods and who does not wish to gain weight, consumes comparatively small quantities of cereal products and is little affected by the enrichment program. Many such people, however, do subsist on diets that are inadequate in vitamin content to meet their requirements. To protect them against the de-

TABLE 4

SUPPLEMENTAL VITAMIN PREPARATIONS

VITAMIN	DAILY DOSAGE (RANGE)
Basic formula*	
Vitamin A (synthetic or natural)	1500-5000 U.S.P. units
Vitamin D	400-1000 U.S.P. units
Thiamine (hydrochloride or mononitrate)	1.0-2.0 mg.
Riboflavin	1.0-3.0 mg.
Niacinamide	5.0-20.0 mg.
Ascorbic acid	50.0-100.0 mg.
Expanded formula (add to basic formula)	
Pyridoxine hydrochloride	0.5-2.0 mg.
Calcium pantothenate (or PANTHENOL®)	5.0-15.0 mg.
Folic acid	0.20-0.30 mg.
Vitamin B_{12}	1.0-2.0 μg.
Vitamin E	2.5-10.0 mg.
Pregnancy formula (add to expanded formula)	
Vitamin K	1.0-2.0 mg.
Preparations of water-soluble vitamins	
Remove vitamins A, D and E from the expanded formula	

*This formula contains all those vitamins for which the Food and Nutrition Board has recommended a daily dietary allowance.

velopment of vitamin deficiencies, it is necessary to resort to the use of supplemental vitamin therapy in addition to diet instruction and nutrition education. This is particularly true for individuals who obtain most of their meals in commercial eating places, those with dietary idiosyncrasies, and those who have restricted or unbalanced diets for any reason.

It must be emphasized that supplemental vitamin therapy is a means of protecting the individual against the development of vitamin deficiency states and is a means of maintaining normal tissue reserves against the demands of unusual stress situations, such as illness, injury and pregnancy. Although in some instances such therapy may be curative of vitamin deficiency states, cure of existing disease is not the prime purpose or justification for supplementation. More satisfactory regimens are available.

Generally, the recommended daily dose of pharmaceutical vitamin preparations intended for supplemental therapy contains all the vitamins listed in table 1 in amounts at least equal to one-third and not greater than twice the recommended dietary allowances. As a rule they also contain significant amounts of vitamin B_6, pantothenic acid, folic acid and vitamin B_{12}. Other vitamins, minerals and intrinsic factor sometimes are included. Most supplemental vitamins are put up so that one daily dose generally is sufficient for the purposes just indicated. Examples of multiple-vitamin formulas satisfactory for supplemental purposes are given in table 4.

Supportive Vitamin Therapy

Disease and injury may increase vitamin requirements; interfere with their ingestion, absorption or utilization; or increase elimination. The majority of therapeutic diets outlined in hospital manuals do not supply the nutrients necessary to maintain good nutrition during the acute phase of an illness, and insufficient attention is given to the extra requirements for the convalescent and rehabilitative phases of medical care.[6] Prolonged convalescence is just as much a physiologic drain on the individual as is acute disease and injury.

Supportive vitamin therapy falls into three general categories: preparation, maintenance and rehabilitation.

Preparation—Prior to elective surgery or other predictable stress situations, it is advisable to bring the patient into as good a state of nutrition as possible. Of course, if the patient has been maintained on a good diet with an adequate vitamin intake, there is no need to increase vitamin consumption further prior to operation. When this is not true or in cases in which it is not possible for the physician to ascertain the patient's true nutritional status, it is advisable to administer multiple-vitamin preparations preoperatively. Vitamin K should be given if the prothrombin time is found to be prolonged.

Since the duration of prestress preparation generally is short, it is recommended that therapeutically effective amounts of the vitamins be given during this period. This may be

TABLE 5

THERAPEUTIC VITAMIN PREPARATIONS

VITAMIN	DAILY DOSAGE (RANGE)
Basic therapeutic formula*	
Vitamin A	10,000-50,000 U.S.P. units
Vitamin D	400-1000 U.S.P. units
Thiamine	5.0-10.0 mg.
Riboflavin	7.0-15.0 mg.
Niacinamide	50.0-150.0 mg.
Ascorbic acid	150.0-400.0 mg.
Water-soluble vitamins (stress formula)	
Thiamine	5.0-10.0 mg.
Riboflavin	7.0-15.0 mg.
Niacinamide	50.0-100.0 mg.
Pyridoxine	5.0-10.0 mg.
Calcium pantothenate (or Panthenol)	20.0-50.0 mg.
Folic acid	0.20-0.30 mg.
Vitamin B_{12}	2.0-5.0 μg.
Ascorbic acid	250.0-400.0 mg.
Expanded therapeutic formula† (add to stress formula)	
Vitamin A	10,000-50,000 U.S.P. units
Vitamin D	400-1000 U.S.P. units
Vitamin E	25.0-50.0 mg.

*This formula contains all those vitamins for which the Food and Nutrition Board has recommended a daily dietary allowance.

†Vitamin K is given separately when indicated.

accomplished by increasing the daily intake of supplemental vitamin preparations (table 4) to four or more or by resorting to the daily use of one or more therapeutic preparations (table 5). The exact quantities and type of preparation used will be determined by the patient's nutritional status, as judged by the attending physician.

Maintenance—Well-nourished individuals manifest a negative nitrogen balance following injury or the onset of illness. Chronically ill and malnourished patients resist any further nitrogen loss.[6] This loss of body nitrogen, which may be very large, is accompanied by some loss of some of the water-soluble vitamins, particularly riboflavin.[7] More striking, however, is the effect of such physical stress in diverting the B vitamins, vitamin C and vitamin A from the plasma and urine to the tissues or to storage depots. The significance of this shift of vitamins from the plasma to the tissues is not known, and the fact that the plasma levels of these substances may be low does not necessarily indicate that there is a deficiency of them in the body. Experiments with rats[8] have shown that in the instance of vitamin A the drop in the serum level which occurs in the presence of infection is accompanied by a decrease in liver content and concentration of the vitamin and by some loss of vitamin A in the urine. Much more important from the practical standpoint is the increase in nutrient requirements caused by the increase in metabolism that follows injury and the onset of illness, combined all too frequently with inadequate hospital diets (general and special, orally and parenterally administered) and often associated with anorexia, diarrheas or absorption defects.

In the catabolic stages of acute illnesses and following injury it may be extremely difficult, if not impossible, to bring the patient into positive nitrogen balance and to maintain the blood vitamin values at prestress levels. It has been demonstrated, however, that the deleterious effects of the catabolic stage can be minimized by a diet adequate in calories and rich in high-quality protein and vitamins, and it is generally conceded that such a regimen shortens the period of convalescence.[6] Suitable formulas for oral or parenteral use are given in table 5.

Rehabilitation—During convalescence, nutrition therapy is directed toward the replacement of nutrient losses in the previously well-nourished individual and toward establishment of optimal nutritional status in the formerly malnourished person. This process involves the supplying of protein, calories, vitamins and other nutrients in liberal amounts. Generally, the more rapid and complete the nutritional rehabilitation, the shorter the period of convalescence.

If the disease or injury was mild and the patient was previously well nourished, supplemental amounts of the vitamins (table 4) generally will suffice. If the disease or injury was severe or of long duration or if the patient was malnourished, it is advisable to administer therapeutic amounts of the vitamins (table 5)

until convalescence is well established and the patient has attained good nutritional status; then, a supplemental vitamin preparation should be continued for a protracted period. This general rule will be modified by the attending physician, depending on such factors as the persistence of defects in absorption and utilization, poor dietary habits, restricted therapeutic diets, and abnormally high metabolic requirements.

Specific Vitamin Therapy

The treatment of vitamin deficiency diseases requires an accurate diagnosis, intensive therapy with those vitamins the absence or deficiency of which is immediately responsible for the patient's signs and symptoms, adequate supportive therapy, and the eradication or minimization of conditioning and precipitating factors.

It is recommended that therapeutic polyvitamin preparations (table 5) be used, plus additional quantities (5 to 10 times the recommended daily dietary allowance) of the vitamin specific for the predominating deficiency. Orally administered therapy generally is the method of choice whenever feasible. Vitamin B_{12} and vitamin K deficiencies are exceptions to this rule, although satisfactory management by proper orally administered therapy is possible in most cases.

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Postgraduate Clinical NOTES

140. TRANSFER OF VITAMINS FROM MOTHER TO FETUS

It is interesting to note that the fetus, despite its initially higher levels of concentration, has the capacity to draw not only vitamin B_{12} but other vitamins, such as ascorbic acid, B_1 (thiamine), and B_6 (pyridoxine), and also nutrients such as iron from the mother. If this phenomenon were one of a physiochemical nature, one might expect glucose and insulin to be divided in a similar manner between fetal and maternal blood. This, however, was not the case in our study. Furthermore, the work of Migeon and associates indicated that maternal blood contained more 17-hydroxycorticosteroids than fetal blood. Thus, taken as a whole, these data would indicate that the differences in the vitamin B_{12} serum gradient will have physiological meaning and specificity and that this phenomenon is not primarily a chemical one.

B. F. Chow and K. Okuda, Transfer of vitamins from mother to fetus, *Journal of the American Medical Association*, January 30, 1960, pp. 422-426

CLINICOPATHOLOGIC CONFERENCE

Report From Veterans Administration Hospital, Hines, Illinois

Edited by William J. Gillesby, M.D., Assistant Chief, Surgical Service

Case Report

A 64 year old white hotel clerk was admitted to Hines Veterans Administration Hospital on September 10, 1958. He had been in good health until the onset seven weeks previously of a hacking, nonproductive cough associated with a sensation of tightness in the upper midchest and throat. Moderate loss of appetite and a slight loss of weight had been noted during this time. The patient also complained of having had a backache for "quite some time," for which a heating pad had been applied locally. Fever of 100° F. was noted on the day before admission; however, the patient denied having had previous fever, sweats or chills.

The patient's history was unremarkable, except that at age 32 he had had "bad blood," which had been treated with injections. He had smoked one-half of a package of cigarettes daily for many years, and occasionally he had drunk beer or a highball. He had had an uncomplicated inguinal herniorrhaphy on the left side.

On admission, the patient's temperature was 100° F., pulse 86 and regular, and blood pressure 120/80. He did not appear to be acutely ill. The head, neck and ears were normal. The systemic review disclosed a recent decrease in visual acuity and occasional blurring of vision; otherwise, results were negative. Both pupils reacted sluggishly to light, and the right pupil was "irregular." The mouth was edentulous, with the exception of a few lower teeth in poor condition. The tongue was dry and coated, and the pharynx was slightly inflamed. The chest was symmetric and the lungs were clear except for a few crepitant rales in the left base. The heart was not enlarged and the rhythm was regular. The A_2 sound was slightly louder than the P_2 sound; no murmurs were heard. Except for the healed scar of the inguinal herniorrhaphy on the left side, results of abdominal examination were negative. The genitalia, rectum and prostate were normal. Bilateral healing minor burns of the skin of the lumbar area were present. Neurologic examination yielded normal results, with the exception of bilaterally hypoactive knee jerks and a hypoactive right ankle jerk.

Laboratory data—Three urinalyses made during the patient's first week of hospitalization showed acid reaction, a specific gravity of 1.015 to 1.020, zero to trace albumin, no sugar, zero to seven white blood cells, and up to four to six red blood cells per high-power field. Serologic studies gave negative findings. Hematocrit was 40 per cent and hemoglobin was 13.5 gm. The white blood cell count was 8600, with 69 neutrophils, 29 lymphocytes, and two eosinophils. The erythrocyte sedimentation rate was 27 mm., and nonprotein nitro-

gen was 30.3 mg. per cent. Fasting blood sugar was 108 mg. per cent.

A posteroanterior x-ray of the chest made three days prior to admission revealed elevation of the left hemidiaphragm and a homogeneous shadow (believed to represent breast shadow) obscuring the left costophrenic sinus. The lung fields were clear. The aortic arch appeared slightly widened and contained calcific densities. Another posteroanterior chest x-ray on September 10 revealed similar findings. Anteroposterior and lateral views of the lumbosacral spine showed minimal hypertrophic osteoarthritic changes throughout the lumbar spine; multiple metallic densities were seen in both iliac regions.

The gallbladder was not visualized by a cholecystogram. The upper gastrointestinal series gave normal findings. An electrocardiogram on September 15 showed sinus rhythm, depressed ST wave in V_4, V_5 and V_6, an inverted T wave in lead III, and a flat T wave in the aVF (augmented unipolar foot) lead. Sputum culture showed the presence of *Neisseria catarrhalis*.

Hospital course—The patient was treated with 300,000 units penicillin G procaine twice daily and the usual supportive measures. Administration of liberal quantities of orally and parenterally given fluids resulted in a recorded daily urinary output of 2000 to 4000 cc. throughout the hospital course. A spiking temperature, with daily elevation to 101 or 102° F. orally, was noted during the first three weeks of hospitalization. The basal rales disappeared within a few days. Episodes of mental confusion occurred at this time and acute urinary retention necessitated use of an indwelling catheter. A generalized maculopapular eruption occurred on the eighth hospital day. The administration of penicillin was stopped, and treatment with 250 mg. tetracycline four times daily was started. The skin lesions cleared spontaneously within a period of a few days.

On the ninth hospital day, the patient became semicomatose; he had marked nuchal rigidity and a positive Kernig sign. A traumatic lumbar puncture yielded a small amount of bloody spinal fluid from which was cultured hemolytic *Staphylococcus pyogenes* var. *aureus*, coagulase positive, sensitive to erythromycin in vitro. The white blood cell count was 20,400, with 98 per cent neutrophils. Intravenously administered erythromycin (1.5 gm. daily) was started on the eleventh hospital day. By the fourteenth day, the patient was lucid; he was taking fluids by mouth, and 500 mg. erythromycin could be given orally four times a day. The patient also received 0.5 gm. streptomycin twice daily from the fourteenth to the twenty-first hospital day. He continued to improve; his temperature became normal on the twenty-second day and remained normal for seven days.

The patient was gradually ambulated, but he remained weak and appeared pale and chronically ill. The hemoglobin was now 9.5 gm. and the white blood cell count was 10,700. Erythromycin was discontinued on the twenty-eighth day. On the following day, the patient's temperature was 100° F.; during the remainder of the hospital course, an occasional elevation to 100° F. (rarely 101° F.) occurred.

Although the patient's general condition apparently improved gradually, several problems persisted. Urinary retention followed removal of the indwelling catheter on the thirty-sixth day. However, a urologist found the abdomen, genitalia and prostate normal. Cystoscopy was deferred, pending further improvement in the general condition, and it was thought that the patient had a neurogenic bladder secondary to meningitis. He also continued to complain of back pain, for which general conditioning exercises and salicylates were prescribed.

The white blood cell count on the forty-first hospital day was 19,200; hemoglobin was 9.5 gm. An electrocardiogram revealed diphasic T waves in leads I, II, aVF, V_4, V_5 and V_6; an inverted T wave in lead III; and a sinus tachycardia with occasional premature atrial contractions. A blood culture on the forty-fourth day yielded hemolytic *Staph. pyogenes* var. *aureus*, coagulase positive. The nonprotein nitrogen was 32.5 mg. per cent.

On the forty-eighth hospital day, the patient suddenly became acutely short of breath. Examination revealed severe dyspnea, restlessness, cyanosis and a diffuse diaphoresis. There

were bilateral basal moist rales, and the heart rate was 160 per minute and regular. The electrocardiogram showed elevation of the ST segments in leads II, III and aVF and accentuation of the previously described ST and T wave changes. Despite digitalization and the administration of oxygen, aminophylline and a mercurial diuretic, the patient failed to improve; the state of shock became increasingly severe, and he died two hours after the onset of dyspnea.

Discussion

DR. ROBERT O. LEVITT (associate professor of medicine, University of Illinois College of Medicine, Chicago, and attending physician, tuberculosis service, Hines Hospital): The first physical examination of this patient following his admission to the hospital revealed no remarkable findings. Evidently, there were no symptoms which might have indicated the necessity of an extensive neurologic examination, and the fundi apparently were not checked on admission. The laboratory data at the time of admission showed a few findings in the urine, including red and white blood cells, which I do not know how to evaluate. Rarely is a patient admitted to the tuberculosis service without albumin and red and white blood cells in the urine. Subsequent urinalyses in this case revealed no findings. This patient had no anemia and the differential blood count was normal. The elevated erythrocyte sedimentation rate indicated that he had a chronic illness.

There were some findings on the x-rays of the spine and chest, and before attempting to evaluate this case further, I would like to hear a review of those findings.

DR. MIRIAM LIBERSON (physician in charge of diagnostic x-ray): We would consider that the x-ray findings of the chest in this patient were essentially negative in regard to acute or chronic lung disease. The anteroposterior and lateral views of the lumbar spine were equally noninformative as far as its being a possible site of a pathologic condition. The patient complained of low back pain. Except for mild degenerative spurring along the anterior margins of the lumbar vertebral bodies, there were no significant findings. There was appreciable calcification observed in the abdominal aorta.

DR. LEVITT: The x-rays which were made of the spine and chest were not helpful in making a diagnosis in this case. I would like to make a plea here for the routine use of lateral views when chest x-rays are requested. A posteroanterior view in a chest x-ray is not a complete examination; there are many structures behind the heart and below the diaphragm that we miss if we do not make a lateral view.

I think we cannot attach too much importance to the results of the first electrocardiographic tracing in this case, which showed a semihorizontal heart with some slight ST segment depression of a rather nonspecific character in V_4, V_5 and V_6. The T wave was inverted in lead III and depressed in aVF. The tracing taken more than a month later showed considerable changes. The electric axis was changed; the QRS wave in lead III had become elevated, while the T wave was still inverted. The ST segment depression and diphasic T waves had progressed in leads V_4, V_5 and V_6, suggesting some element of ventricular strain on the left side. The T waves also were diphasic in leads I and II. The electrocardiogram made on the day the patient died showed similar findings, but the changes were more marked. The findings noted, particularly in leads III and aVF, suggested an acute posterior myocardial infarction as a terminal event.

In reviewing briefly this patient's course, we find that he responded well to antibiotics and fluids for a short period. Although he had a fever for several days, the chest symptoms disappeared. However, the neurologic episodes became more apparent; periods of mental confusion developed and acute urinary retention necessitated use of an indwelling catheter, even though genitourinary examination gave normal results. A rash which appeared on the eighth day of hospitalization cleared when penicillin therapy was discontinued, so we assume that this indicated an allergy to penicillin. Meanwhile, tetracycline was started, but signs of meningitis developed in a few days.

Culture of a small amount of bloody spi-

nal fluid from a traumatic lumbar puncture showed the presence of hemolytic *Staph. pyogenes* var. *aureus*. I do not know whether or not this was traumatic. Perhaps it was not; maybe the patient *had* a bloody spinal fluid. The patient became rational and responded well to intravenously administered erythromycin; however, in spite of this treatment and the addition of other antibiotics, he continued to have a low-grade fever and was pale and anemic. His temperature rose on discontinuance of erythromycin, and it remained elevated for the remainder of his hospitalization. He complained of back pain; although this was not localized, I assume that it was in the lumbosacral spine since we have x-rays of that region.

Hemolytic *Staph. pyogenes* var. *aureus* was again isolated in a blood culture on the forty-fourth hospital day. There is no reference to the development of petechiae, cardiac murmurs or anything that would suggest peripheral emboli. The terminal event was an acute cardiac condition, with dyspnea, restlessness, cyanosis, rales and tachycardia.

Thus, the symptoms in this patient seem to suggest a chest condition despite the absence of pathologic findings in the chest. We also must consider that meningitis developed after the patient was hospitalized. Because he became more acutely and much more seriously ill within a short time after entering the hospital, it seems that the hemolytic *Staph. pyogenes* var. *aureus*, coagulase positive, was present at the time of hospitalization. However, there was no report of any bacteriophage typing, so we cannot be sure that he was not infected with the bacteria after entering the hospital.

What caused the meningitis? This disease does not just develop from a clear sky and, certainly, staphylococcal meningitis has a focus somewhere in the body. There was no sign of an abscess involving the vertebral column, nor were there any reports of masses or pain, which would lead one to think that there was an intraabdominal abscess.

Could this man have had a small lung abscess that was not visualized by x-ray, or did he have a bronchiectasis which caused a hematogenic dissemination of staphylococci and the development of a staphylococcal meningitis? There also is a possibility that the patient may have had a small focus near his back or in his lungs which we could not visualize and which caused a chronic brain abscess that ruptured and resulted in the meningitis that was discovered after he entered the hospital.

There is not sufficient evidence here to indicate which of these conditions might have been present. The neurologic findings on admission, the decrease in visual acuity, and the occasional blurring of the vision prior to admission indicate that the patient may have had a brain lesion before he was hospitalized. Thus, I would state that there probably was a focus of infection somewhere in the patient's body, possibly in his lung, with brain abscess and meningitis. He had a staphylococcal blood infection. Although there is nothing in the protocol to indicate that an acute staphylococcal endocarditis was present, it might have been. No murmurs were mentioned, and I believe that death was caused by an acute cardiac accident.

DR. MYRON E. RUBNITZ (chief, laboratory service): By "acute cardiac accident" do you mean the changes compatible with the myocardial infarct seen on the electrocardiogram?

DR. LEVITT: Yes.

DR. ROBERT LAPPE (resident, medical service): Do you think that this patient's teeth might have been a focus of abscess following administration of antibiotics? Is it possible that an alveolar abscess might have spread and caused a septicemic meningitis?

DR. LEVITT: That thought never occurred to me. I have been singularly unimpressed in general with dental abscesses as foci of any type of disease, including arthritis. I had my original medical training during the time that the medical profession had stopped extracting teeth for arthritis and had gone quite the other way. A dental abscess *could* have been the source of infection in this patient—anything could have been—but this possibility had not occurred to me at all.

DR. GLOUCESTER PRICE (assistant section chief, hematologic and metabolic service): This patient came into the hospital with fever

f obscure cause and was given penicillin dur-
ng his initial eight days or so. At the end of
at time, the more overt manifestations of
eurologic change occurred. Would you please
omment, first of all, about the empiric peni-
illin therapy which is given in the presence
f fever of obscure cause, and, secondly, as
o whether or not there might have been any
elationship between this therapy and the sub-
equent neurologic changes which evolved?

DR. LEVITT: I think we all have been very well indoctrinated with the undesirability of giving antibiotics indiscriminately; I am sure you have heard of it more than once and you have read it a hundred times. I am positively *not* in favor of treating fever with antibiotics, but of using them to treat diseases caused by specific organisms. I already have alluded to your second point. I do not know whether or not the staphylococcal infection in this patient developed after he was hospitalized; however, after reviewing his course and after considering the fact that he had been ill prior to admission, I believe that although the penicillin probably did him no good the other infection antedated his hospitalization.

DR. ARMAND LITTMAN (chief, medical service): Dr. Levitt, are you satisfied with the adequacy of the therapy for an established serious staphylococcal infection?

DR. LEVITT: No, I am not. I was just following the protocol here. I think it has been pretty well established that with our erythromycin drugs resistance appears rather rapidly; these drugs rarely are of value for more than four or five days before resistant organisms appear. I would think that no disease requires more effective treatment with about everything we have than does a systemic staphylococcal infection. I am referring to some of our newer drugs, such as kanamycin and vancomycin, particularly where a meningitis is concerned. These drugs contain much less resistant factors and possibly more therapeutic factors. I would not want to rely on erythromycin alone as the therapy of choice. I do not know what the studies of resistance in this patient showed. I assume that he had a strong sensitivity to streptomycin, but that is rarely the drug of choice in treating a staphylococcal infection. It may have been given because someone thought there must have been a tuberculous focus hiding behind all of this.

DR. JAMES NAATZ (resident, general medicine): Would the fact that this patient had chronic pulmonary congestion and chronic back pain and that anemia developed later suggest a possible myeloma?

DR. LEVITT: I do not find anything that would make me consider that diagnosis. As has been indicated, the workup that we have here was not complete, but I would be singularly unimpressed with myeloma as a diagnosis in this case.

DR. EDWARD L. BUSCH (senior resident, general surgery): Dr. Levitt, you mentioned that antibiotic therapy might not be adequate and that other drugs might be given. In the protocol, it is stated that three or four days after the onset of treatment with erythromycin, the symptomatology in this patient cleared; approximately nine days after therapy with erythromycin was started, the patient became afebrile and remained so for seven days, after which the antibiotic was no longer used. I would like to ask you what method you use to know when antibiotic therapy is no longer effective.

DR. LEVITT: When the erythromycin was discontinued the patient "blew wide open" and another positive blood culture was obtained at that time.

DR. BUSCH: How do you know the antibiotic caused this?

DR. LEVITT: I do not think a systemic staphylococcal infection will develop in a patient who thrives on as poor a drug as erythromycin. Generally speaking, if you are going to rely on one drug, one with which resistance does not appear rapidly again, you might use something like chloramphenicol. We know, and I think it has been well documented, that resistance to erythromycin will appear very rapidly; you just cannot rely on that drug alone to clear up any staphylococcal infection. What this man probably had was a suppression of his infection; the erythromycin kept it from spreading again. As soon as the suppressive influence was lifted, the full effect of the hematogenic staphylococcal infection devel-

oped. I would not rely on erythromycin for more than three or four days in any severe infection.

DR. WILLIAM DONNELLY (hematologic and metabolic section chief): In my experience, erythromycin has been effective for about two weeks; if the infection is of such severity that it lasts two weeks or more, you will have to run the gamut of drugs, starting with chloramphenicol and then proceeding to vancomycin and the others.

DR. MYRON E. RUBNITZ (chief, laboratory service): This case presents two separate pathologic findings—one in the heart and the other tying together all of these various foci of infection which Dr. Levitt mentioned. The death of this patient probably can be attributed to the heart, as Dr. Levitt has accurately told you.

The heart showed a complete occlusion of the posteriorly thinning branch of the right coronary artery; however, there was no recent thrombus in this vessel, so it is difficult to state that this patient died of an acute coronary occlusion. Neither did he have a recent myocardial infarct demonstrable either grossly or microscopically. However, it is well known that sudden death can occur from an old occlusion without evidence of a recent thrombus and without changes in the myocardium.

The lungs showed minimal but important changes, particularly in the right middle and lower lobes, where there were small areas of nodular firmness. The kidneys showed multiple small abscesses throughout.

The greatest focus of all was in the region of the fourth and fifth lumbar and the first sacral vertebrae, where there was not only soft tissue involvement but also abscesses in the bodies of those vertebrae. The material was studied and the culture again showed a hemolytic *Staph. pyogenes* var. *aureus*, coagulase positive.

A very low-power photomicrograph through one of the areas of the vertebrae showed a quite obvious small abscess with extensive inflammatory infiltrate. A higher-power view showed the abscess with a spreading of the inflammatory component around it. An even higher-power view showed that it was indeed frank pus, with myriads of polymorphonuclear leukocytes and cellular debris.

A low-power view in the area surrounding the vertebrae showed what appeared to be a fibrocartilaginous area that, I think, might have represented the partial wall of the abscess. Again, inflammatory cells were seen. In the area adjacent to the vertebral column, with the nerve roots extending from it, inflammatory involvement was present. From the granulationlike tissue—new blood vessels—which was seen, it was evident that this was not a recent infection and that it had been present for quite some time. This extensive fine type of infection also was seen around the frank abscess.

The same type of abscess and glomeruli were noted in a section through the kidney. Other kidney sections showed evidence of chronic pyelonephritis; however, it was not of a sufficient severity to be necessarily the focus of infection. A section of the lung also showed inflammatory infiltrate, but it was confined to the right middle and lower lobes and was not seen in random sections through the lung; there also were a number of abscesses.

Of course, this case emphasizes the tremendous problem of staphylococcal infections. From the areas around the abscess, seen in sections through the vertebral region, it was evident that this patient had a chronic infection and that it did not develop after he entered the hospital. Sections through the kidneys also showed this to be an older infection than one which could have developed during the immediate hospital admission. Where the primary focus of infection was, we cannot say. It is possible that it could have been anyplace and that it might have been cured, if you want to use the term, from the antibiotic treatment which the patient received. The focus might have been in the throat, since the patient complained of a sore throat when he came into the hospital. It could possibly have been in the genitourinary tract or in any one of a number of places. However, I agree that many aspects of the examination of this patient were unfortunate; for instance, no urinalysis was made as this condition progressed. We hope that the urinary findings that were reported when he

was admitted were indeed true and that other urinalyses were correct. To do one urinalysis and then to dismiss the advisability of doing others on the basis of their not being important is a practice which proved foolhardy in this case.

I believe that this patient's death was not related to the staphylococcal infection, but what underlying condition this brought about, I do not know. I think death was caused by the coronary occlusion.

Many questions could be raised in this case, particularly those referable to the x-rays of the lumbar spine. Why did not these abscesses show up in some way? Could there have been abscesses in bone which were not viewed by the x-ray?

DR. LIBERSON: It is a known fact that radiologic findings in osteomyelitis have changed their appearance completely since the institution of antibiotic therapy. Before the advent of antibiotics or in untreated cases, one might have expected to see radiologic changes when microscopically there were abscesses in bone likely due to infection; however, with antibiotic therapy those findings are either contained or controlled, with the result that positive x-rays are usually markedly delayed or completely absent. In a treated case of chronic osteomyelitis, x-ray findings may be totally absent. This absence of x-ray findings refers chiefly to the long bones. Osteomyelitis in the spine is particularly difficult to diagnose; the changes have to be considerable, with definite bone abscesses that erode the bony substance or collapse the vertebral bodies. On gross evaluation of the findings in the films made of this patient, which were taken seven weeks prior to his death, there was no evidence of any bone destruction by direct findings or by an indirect incidence due to collapse of the vertebral body.

DR. LIONEL M. BERNSTEIN (assistant director, professional services for research): Would you agree that the presence of a chronic pyelonephritis would make this the most likely initial source of the entire problem in this patient?

DR. RUBNITZ: It certainly is a great possibility which I cannot rule out; however, the sections through the kidney indicated that this was not the old ascending pyelonephritis that is caused by long-smoldering lower urinary tract infections. It was not the hydronephrotic type of kidney; it was more a disseminated abscess *with* some chronic pyelonephritis—a different picture from that we ordinarily find.

DR. BERNSTEIN: I also would like to comment on the fact that the nonprotein nitrogen was still normal on the forty-fourth day, which again indicates that since the nonprotein nitrogen does not become elevated until below 20 per cent of function, it is quite possible to have diffusely involved abscess of the kidney bilaterally and still have a normal nonprotein nitrogen.

DR. RUBNITZ: That is true, but it also points to the fact that this probably was not a severe chronic pyelonephritis; if it had been, the patient probably would have had a higher nonprotein nitrogen.

DR. OSCAR HARMOS (staff physician, laboratory service): Did the underlying septicemia have anything to do with triggering the coronary occlusion?

DR. LEVITT: It might have been responsible. Prolonged sepsis, marked tachycardia and severe anemia are sufficient to cause either an acute or a chronic myocardial failure. This patient might have died at some future time of a cardiac condition; however, I think that his death was immediately related to the fact that the infection caused a strain on his completely insufficient coronary artery system.

Self-help Devices:
Transfer On and Off a Toilet

EDWARD W. LOWMAN AND HOWARD A. RUSK

Institute of Physical Medicine and Rehabilitation
and the Arthritis Self-help Device Office*

New York University-Bellevue Medical Center, New York

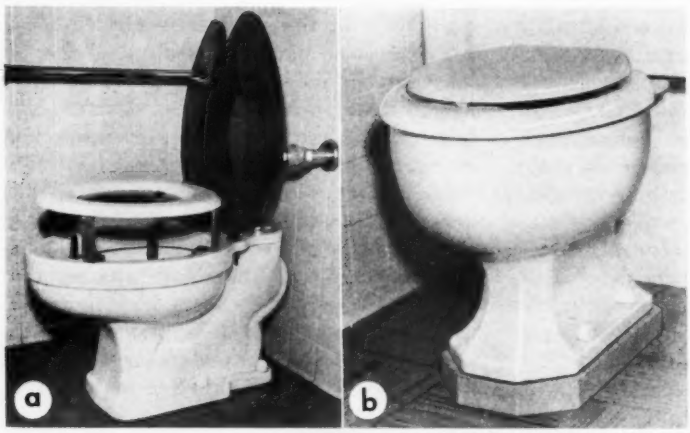

FIGURE 1. Standard-height toilet seats often are a problem for ambulatory patients with involvement of hip or knee or both. Raising the height of the toilet seat, therefore, becomes an important consideration. This may be done in several ways.

a. An easily installed elevated seat is available in lifts of 4, 5 and 6 in. from most local hospital supply houses. Prices range from $12.50 to $15.00.

b. For a permanent arrangement, the toilet stool may be raised on a small platform about the same size as the base.

FIGURE 2. Those planning a new home or new bathroom fixtures should investigate the wall-hung toilet. Further information can be obtained from American-Standard, Plumbing and Heating Division, 40 West 40th Street, New York 18.

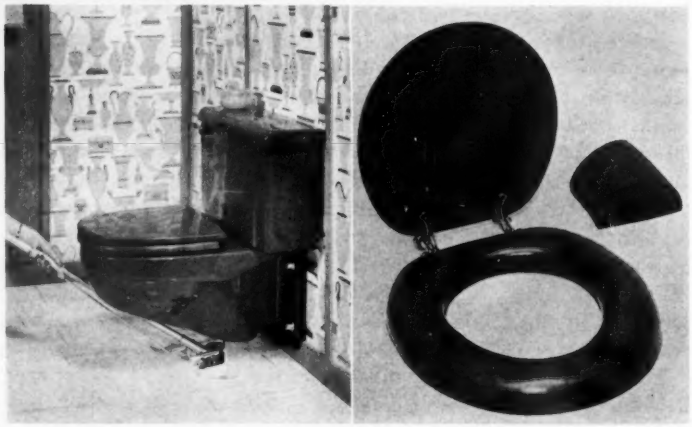

FIGURE 3. Soft toilet seats, padded with sponge rubber and upholstered with washable plastic, are available. The padding also raises the sitting height. Most hospital supply houses sell this item for about $12.00.

*Supported at the Institute by the Arthritis and Rheumatism Foundation.

FIGURE 4. A glider chair with a commode seat will slide over the toilet bowl, adding 3 to 5 in. to the height of the standard toilet. It eliminates the need for armrests for those who need support getting down on and up from the seat. A catalogue may be obtained from Everest & Jennings, Inc., 1803 Pontius Avenue, Los Angeles; American Wheelchair Company, Cincinnati 38, or Invalex Sales, 741 West 17th Street, Long Beach 13, California.

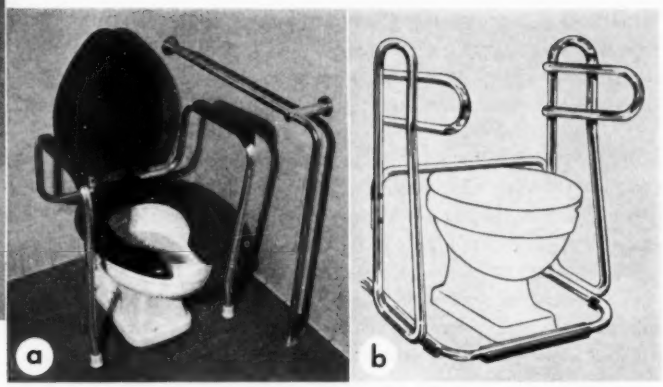

FIGURE 5. Several toilet frames are available for the patient who needs support in getting on and off the seat.

a. This model, which is supported on the floor, is available from Winfield Company "Winco," 1301 Third Street South, St. Petersburg. They also have a model which is supported on the toilet bowl.

b. This unit can be either bolted to the toilet fixture or freestanding. Available from Self-Ease Units, Inc., 1026 Park Avenue, New York 28.

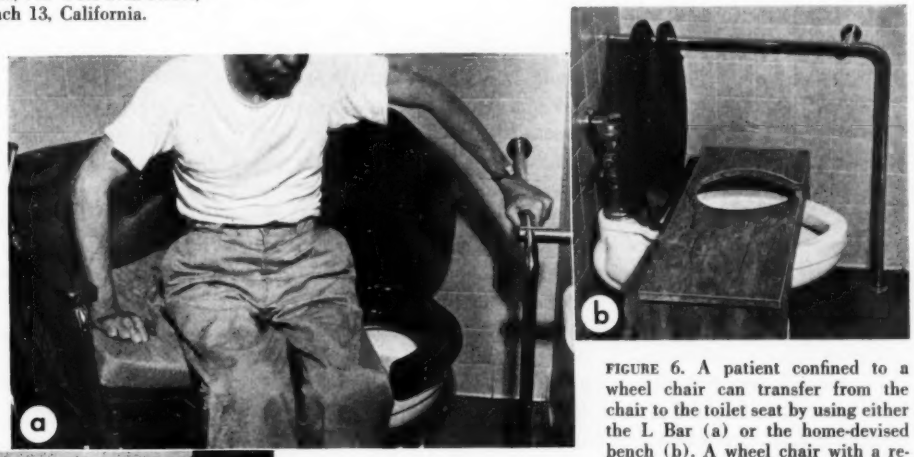

FIGURE 6. A patient confined to a wheel chair can transfer from the chair to the toilet seat by using either the L Bar (a) or the home-devised bench (b). A wheel chair with a removable arm expedites the transfer.

FIGURE 7. When lack of space prohibits transfer sideways, patients can successfully manage by shifting backward from the wheel chair. In this instance, the chair must have a removable back. either button or zipper.

Readers are invited to submit suggestions and ideas for devices they have developed and would like to share with others. Forward all such suggestions and comments to: Editorial Department, POSTGRADUATE MEDICINE, Essex Building, Minneapolis 3.

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THE BRAIN AND NERVOUS SYSTEM

AMONG the outstanding advances in medicine of the last 20 years has been the new knowledge accumulated relative to the brain and the nervous system. Already it is clear that every one of the basic sciences is contributing to a knowledge of the structure, physiology, pathology and disturbances affecting the brain and the nervous system. Bertrand Russell has noted that the perception of an object is a physicochemical event occurring in the cerebral cortex. Evidence has established that electric stimulation can bring about a duplication of an actual experience. Sir Russell Brain,[1] in a notable series of lectures called "The Nature of Experience," has said that nerve impulses and physicochemical changes cannot themselves be seen but are inferences from the appearances which the scientist observes in experiments.

Dr. A. M. Lassek,[2] professor of anatomy in Boston University School of Medicine, has traced the evolution of the human brain from its most primitive state to the modern brain and has correlated this with the evolution of the mind. The cerebrum evolved into an organ which can express wishes, desires, needs, ideals and ambitions, and eventually mental conflicts. The mind of today responds to instability and rapid change by apprehension, fear, dissatisfaction and hostility. Thus, Lassek explains increasing mental illness, juvenile delinquency, economic breakdown and international hostility. "The brain," he says, "is the key to the future and must be made to react in a more healthful and harmonious manner."

The Brain Research Foundation has just made available a compilation of important considerations about the brain and the nervous system in "Molecules and Mental Health," edited by Dr. Frederic A. Gibbs.[3] He says:

> The brain thinks, sees, hears and, most important, understands because of chemical processes that are going on continuously in the 10 billion chemical machines (nerve cells) which populate the universe between our ears. They form the most highly organized system we know of. Chemical supplies for their operation are brought in by the blood stream, and

from these raw materials the brain creates, through an as yet unimagined process, thought, personality, judgment and creative imagery.

This book is a collection of essays dealing with the amines in relation to brain function and behavior and to the control of various neurologic conditions by the use of hormones.

In this issue of POSTGRADUATE MEDICINE a number of essays dealing with neurochemistry, neurophysics, psychopharmacy, the electroencephalogram, and a variety of nervous and mental conditions are assembled to provide for the reader a picture of some of the various fronts on which our knowledge is progressing. Such unsolved problems as relate to multiple sclerosis, Parkinson's disease and juvenile delinquency are here elucidated. As is emphasized by Dr. Falstein, we cannot expect to discover a vaccine against mental illness. The approach to this problem requires not only the work of the psychiatrist but also that of the social worker, the psychologist, the clergy, the sociologist, the anthropologist, the counselor and even the police.

In this series of papers POSTGRADUATE MEDICINE does not attempt in a single issue to elucidate even all that every doctor should know in this field. If it can encourage the doctor to more study and participation in extending still further the boundaries of knowledge, the purpose will have been achieved.

MORRIS FISHBEIN

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2. LASSEK, A. M.: The Human Brain From Primitive to Modern. Springfield, Illinois, Charles C Thomas, 1957.
3. GIBBS, F. A. (ED.): Molecules and Mental Health. Philadelphia, J. B. Lippincott Company, 1959.

CANCER OF THE RECTUM IN OCTOGENARIANS

UNDER this title, Dr. Stuart H. Q. Quan[1] of the Memorial Center for Cancer and Allied Diseases in New York has provided what is probably the first consideration of the incidence of cancer of the rectum in persons more than 80 years of age. He noted that life expectancy at age 80 has increased but little since 1850. Today life expectancy at this age is 6.1 years, contrasted with 5.9 years in 1850. Nevertheless, there are many more octogenarians now than there were 100 years ago.

From 1929 to 1954, 51 patients with adenocarcinoma of the rectum who were 80 years of age or older were seen in the Memorial Center. During the same 25 year period, approximately 4500 patients with malignant tumors of the rectum were seen. Thus, these 51 patients represented only a little over 1 per cent of the total patients. Twenty were women and 31 were men. The most common complaint was bleeding from the rectum, which occurred in more than 40 patients. Constipation and weight loss were also common symptoms. The symptoms which occurred less frequently were diarrhea, rectal pressure or pain, sensation of a mass, rectal incontinence, tenesmus, excessive flatus, passage of mucus, and alternating constipation and diarrhea. Forty patients were treated conservatively with irradiation; occasionally, colostomy was performed, and in two instances there was local removal by surgery. Eleven had radical surgery, such as abdominoperineal resection or posterior resection of the rectum preceded by colostomy. Such serious operations as these have been performed only since 1946.

Thirty of the 40 patients treated conservatively died in less than two years. Of 10 who lived more than two years, the oldest is now 92 years old; nine years have elapsed since the treatment, which consisted of roentgen ray and cautery snare removal of a colloid carcinoma of the rectum. Two other patients lived more than five years. Of 11 patients operated on since 1946, all but two were described as being in good condition or well preserved. The two deaths occurred within 30 days after operation. Two are still living and apparently there is no evidence of recurrent disease after six years. The average period of survival, excluding the surgical deaths, was 45.5 months.

As a result of this experience, which is probably as large as is available anywhere else in this country, Dr. Quan concluded, "These results and the fact that life expectancy at ages 85 and 90 years is, respectively, five and three

and one-half years would seem to indicate that it is reasonable to employ accepted radical surgical methods for removal of rectal carcinoma in selected cases regardless of the patient's age." In selecting patients, it must be determined that the patient is a suitable operative risk and that the tumor is removable without employing the superradical type of operation with extensive lymph node dissection.

MORRIS FISHBEIN

REFERENCE

1. QUAN, S. H. Q.: Cancer of the rectum in octogenarians. Dis. Colon & Rectum 2:355-361 (July-August) 1959.

TWENTY-FIFTH BIRTHDAY OF ALCOHOLICS ANONYMOUS

IN July 1960 Alcoholics Anonymous will celebrate its twenty-fifth anniversary. The organization includes more than 250,000 members and the anniversary will be celebrated by some 10,000 members in a meeting at Long Beach, California. Refreshments will include coffee and soft drinks.

At present Alcoholics Anonymous includes 8000 local chapters in 5,760 communities in more than 80 countries. Such growth as this can only be a recognition of success in achieving its objective. Especially significant is the fact that this movement is completely self-supporting and does not accept outside contributions in any form. It is nonpolitical and is not involved in approval or disapproval of the temperance movement. It does not accumulate property beyond such financial reserves as are necessary to insure its future.

In 1951 the American Public Health Association announced the presentation of a Lasker Group Award to Alcoholics Anonymous "in recognition of its unique and highly successful approach to that age-old public health and social problem, alcoholism." Incidentally, the organization includes a group called International Doctors of Alcoholics Anonymous. The 100 physicians who are members of this group are alcoholics.

MORRIS FISHBEIN

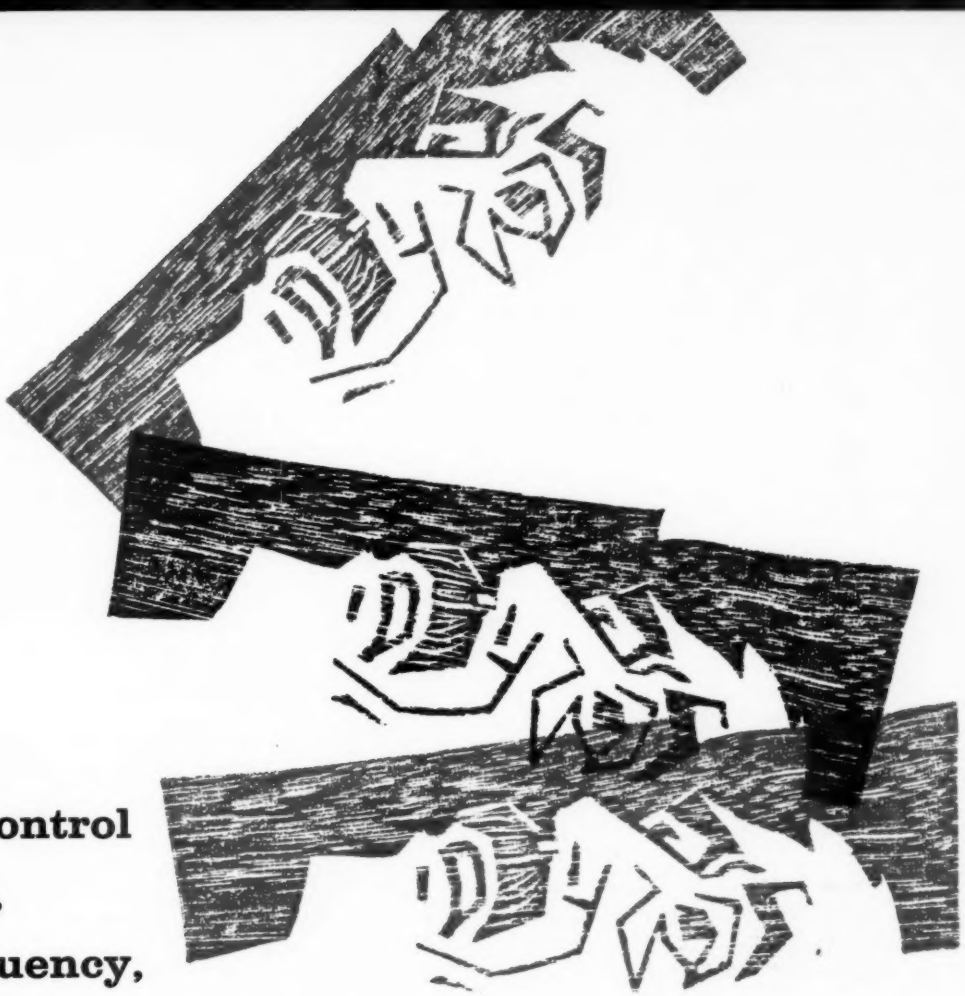
"JOURNAL OF FORENSIC SCIENCES"

UNDER the editorship of Dr. Samuel A. Levinson, a publication called the *Journal of Forensic Sciences* appears quarterly as the official publication of the American Academy of Forensic Sciences. Such subjects as pathology, toxicology, psychiatry, and immunology in relation to crime or death form the basis of most of the discussions, but there also are studies of jurisprudence, criminalism and identification of persons and documents. Recent issues provide material about such exciting topics as anonymous letters, infanticide, the problems of the psychiatrist and psychologist in compensation work, blood-grouping tests in disputed paternity, and the psychodynamics of suicide. Some experiments in determining the accuracy of eyewitnesses indicate that such evidence is usually faulty, and these experiments have led to the recommendation for the adoption of photographic and other objective methods for recording evidence as soon as possible after any untoward incident.

A discussion of the investigation of suicide notes by James V. P. Conway, document analyst for the post office in San Francisco, included the following feeling statement about our presently documented world:

> Today our society whirls giddily in a ticker-tape world of documents. We are carried, glide, and stumble from birth certificate to death certificate with a goodly batch of income tax returns in-between. The mass of documentation, much of it onerous and annoying, with which we are surrounded tends to make our society rather contemptuous of documents. This leads to casual judgments of consequential documents such as the suicide note. Even when an important document such as the suicide note is questioned or disputed, this contemptuous undertone persists, bred as it is of familiarity with reading and writing and the cloak provided by the vast majority of documents which are legitimate. Almost everyone, it seems, is an "expert" on handwriting. Relatives, friends, neighbors, physicians, medical examiners, coroners, policemen, lawyers, criminalists, amateur document examiners—all have "opinions."

MORRIS FISHBEIN



To control fear, frequency, and severity of anginal attacks

Equanitrate*

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EQUANITRATE helps control pain and accompanying anxiety in angina pectoris. It reduces the number and severity of attacks, increases exercise tolerance, and lessens nitroglycerin dependence.

A recent double-blind study† comparing meprobamate, a placebo, PETN, and EQUANITRATE states: "The best results . . . in both clinical and electrocardiographic response, were observed with a combination of meprobamate and pentaerythritol tetranitrate [EQUANITRATE]. . . ."

For further information on prescribing and administering EQUANITRATE see descriptive literature, available on request.

Wyeth Laboratories Philadelphia 1, Pa.

†Russek, H.I.: Am. J. Cardiol. *3*:547 (April) 1959. *Trademark

Supplied: **EQUANITRATE 10** (200 mg. meprobamate, 10 mg. pentaerythritol tetranitrate), white oval tablets, vials of 50. **EQUANITRATE 20** (200 mg. meprobamate, 20 mg. pentaerythritol tetranitrate), yellow oval tablets, vials of 50.

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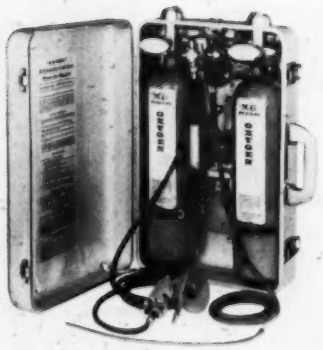
Information published in this department is supplied by the manufacturers of the products described.



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DESCRIPTION: Highly resistant to heat and shock, this 18 lb. unit is designed for emergency rescue work in difficult locations. It may be used as a resuscitator, an inhalator or an aspirator. The head and face mask functions efficiently at distances up to 200 ft. from the oxygen supply. Two breathing mechanisms can be operated simultaneously. The unit can be used with either one or two standard D oxygen cylinders, or it can be operated for an extended period from a large oxygen cylinder by means of a high-pressure hose assembly. The aluminum carrying case measures 21 by 14½ by 7 in.
PRODUCER: National Cylinder Gas Division of Chemetron Corporation, Chicago.

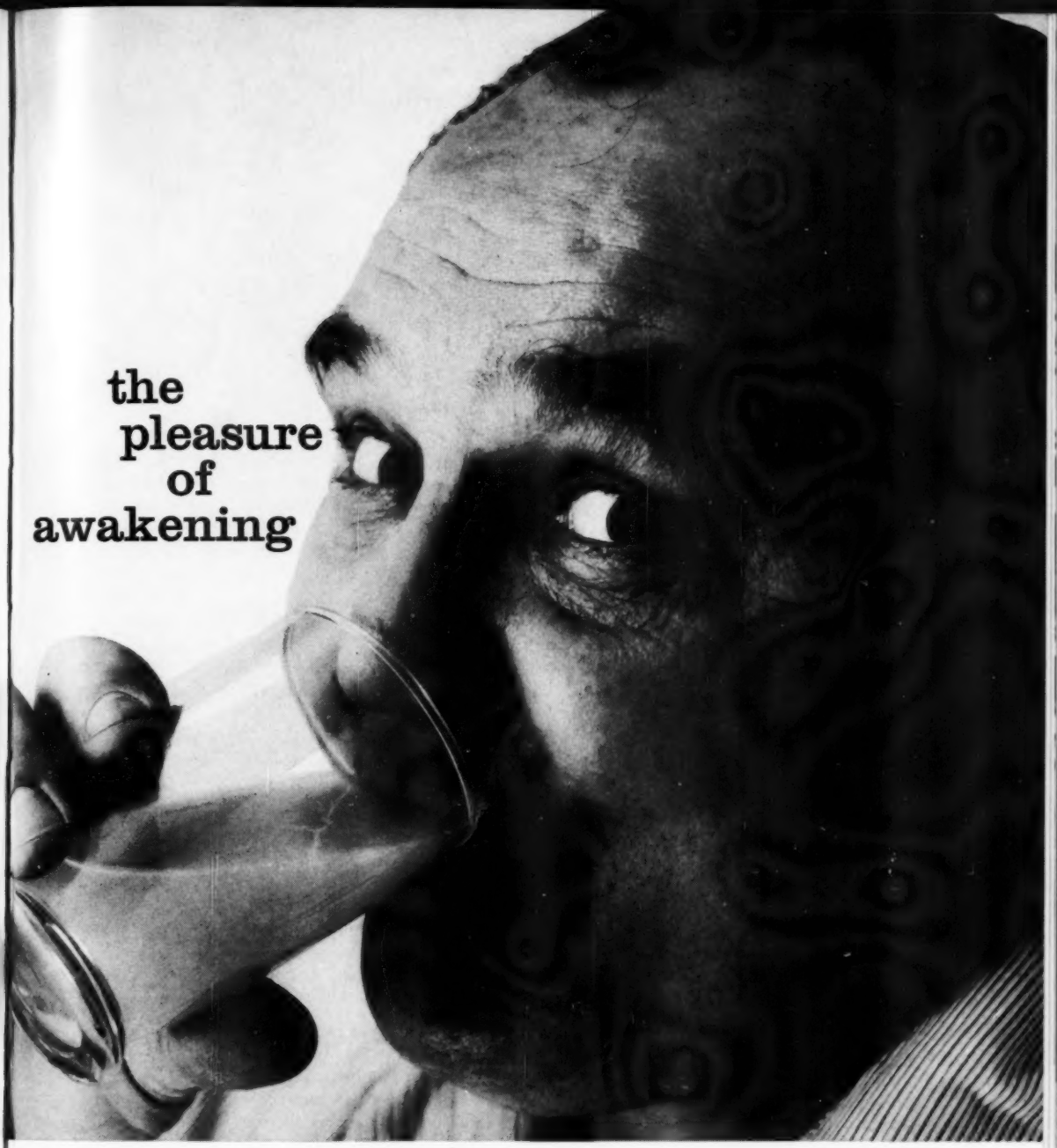
• **DURA-TAB® S.M. AMINOPHYLLINE**

PURPOSE: Sustained antiasthmatic, cardiotonic and diuretic therapy.
COMPOSITION: Each tablet contains 4½ gr. aminophylline.
INDICATIONS FOR USE: Chronic asthma, congestive heart failure, paroxysmal dyspnea, Cheyne-Stokes respiration, angina pectoris, pulmonary edema and certain other conditions in the cardiopulmonary area.
DOSAGE AND ADMINISTRATION: For adults, 1 or 2 tablets every 12 hours; for children less than 10 years of age, ½ tablet every 8 to 10 hours as needed.
HOW SUPPLIED: Bottles of 30, 100 and 250.
PRODUCER: Wynn Pharmacal Corp., Philadelphia.

• **CHEMIPEN**

PURPOSE: Antibiotic.
COMPOSITION: When reconstituted with 35 cc. of water, Chemipen as a cherry-mint-flavored syrup contains 125 mg. Phenethicillin potassium (200,000 units) per 5 cc.; 125 and 250 mg. Chemipen tablets provide 200,000 and 400,000 units Phenethicillin, respectively.
HOW SUPPLIED: Solution in 60 cc. bottles; tablets in bottles of 24.
PRODUCER: E. R. Squibb & Sons, division of Olin Mathieson Chemical Corporation, New York.

(Continued on page A-130)



Free of barbiturate "hangover" after a night of deep, refreshing sleep... this is the promise of Noludar 300. One capsule at bedtime lulls your patient into undisturbed sleep for as long as 6 or 8 hours... without risk of habituation, without toxicity or side effects. Try Noludar 300 for your next patient with a sleep problem. One capsule at bedtime. Chances are he'll tell you

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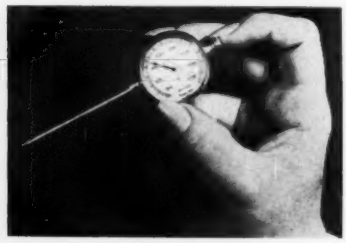
PURPOSE: To treat seborrhea capitis.
COMPOSITION: A highly penetrating, greaseless cream containing:

Allantoin	2%
Coal tar extract	2%
Hexachlorophene	1%

DOSAGE AND ADMINISTRATION: Apply topically three times a day.
HOW SUPPLIED: 2 oz. tubes.
PRODUCER: Reed & Carnrick, Kenilworth, N. J.



• PRECISION CLINICAL THERMOMETER

DESCRIPTION: For either oral or rectal use, this thermometer is shockproof and waterproof and weighs slightly more than ½ oz. It is constructed of a temperature-sensitive combination of metals encased in stainless steel and may be sterilized with alcohol or a disinfectant. The "shaking-down" procedure is eliminated by a button which resets the indicator. The thermometer is available in two lengths, 4¼ in. for standard use and 5⅝ in. for use by veterinarians. A pocket-sized carrying case is included with the instrument.
PRODUCER: Cary Thermometer Company, New York.

• BELAKOIDS TT

PURPOSE: Sustained-action antispasmodic and sedative.
COMPOSITION: Each tablet contains:

Pentobarbital sodium	48.6 mg.
Hyoscyamine sulfate	0.3111 mg.
Atropine sulfate	0.0582 mg.
Hyoscine hydrobromide	0.0195 mg.

DOSAGE AND ADMINISTRATION: 1 or 2 tablets twice daily.
HOW SUPPLIED: Bottles of 100, 500 and 1000.
PRODUCER: Columbus Pharmacal Company, Columbus, Ohio.

• THERMOMATIC® CONSTANT TEMPERATURE BLOCK

DESCRIPTION: Intended primarily for maintaining blood and other body fluids at body temperature, this unit also maintains any laboratory sample at a predetermined temperature between 30 and 50° C. Cast aluminum blocks are used as thermal conductors to a heat-transfer bath of distilled water or a high-boiling organic liquid. A 40 W thermostatically controlled bulb serves as a heating element.
PRODUCER: Scientific and Process Instruments Division, Beckman Instruments, Inc., Fullerton, Calif.

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PURPOSE: Symptomatic treatment of influenza and upper respiratory infections.
COMPOSITION: Each 5 cc. contains:

Tetracycline	125 mg.
N-acetyl-para-aminophenol	120 mg.
Phenyltoloxamine citrate	12.5 mg.

HOW SUPPLIED: 2 oz. bottles.
PRODUCER: Bristol Laboratories, Inc., Syracuse.

• TWISTON® AND TWISTON® R-A

PURPOSE: Antihistamine.
COMPOSITION: Twiston Rotoxamine. Twiston is the active isomer of racemic carbinoxamine.
DOSAGE AND ADMINISTRATION: Twiston, for adults, 1 to 2 tablets three or four times a day; dosage for children is determined according to patient's age. Twiston R-A, for adults, 1 tablet every 8 to 12 hours.
HOW SUPPLIED: Twiston, 2 mg. tablets; Twiston R-A, 4 mg. repeat-action tablets.
PRODUCER: McNeil Laboratories, Incorporated, Philadelphia.

(Continued on page A-132)

In asthma:
a Nephenalin tablet for "air in a hurry"
...and calm...and quiet breathing

For the ambulant asthmatic you can prescribe "air in a hurry" with NEPHENALIN®, a tablet that relieves asthma with nebulizer speed and prevents further attack for hours. Placed under the tongue, the NEPHENALIN tablet quickly releases 10 mg. of isoproterenol HCl, the potent homologue of epinephrine, for immediate opening of the airway. Swallowed, the NEPHENALIN tablet provides theophylline (2 gr.), ephedrine (⅜ gr.) and phenobarbital (⅛ gr.), for sustained protection from asthmatic seizure. Bottles of 20 and 100 tablets. For children: NEPHENALIN Pediatric.

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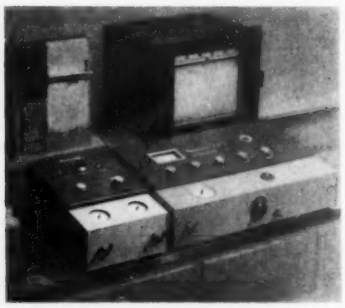
• MOTILYN®

PURPOSE: Prophylaxis and treatment of enteric atonia and ileus.
COMPOSITION: *D*-pantothenyl alcohol.
CAUTION: This drug should not be given sooner than 12 hours after enterokinetic drugs have been discontinued.
DOSAGE AND ADMINISTRATION: For intestinal atonia and abdominal distention, 500 mg. administered parenterally immediately after surgery; dose is repeated two hours later and at 12 hour intervals thereafter as necessary. For paralytic ileus, 500 mg. administered intramuscularly when indicated; dose is repeated at four to six hour intervals as necessary. The dose for children is reduced to approximately 0.1 ml. for each 5 lb. of body weight.
HOW SUPPLIED: 2 ml. ampules, each containing 500 mg. Motilyn, and 10 ml. multiple-dose vials, containing 250 mg. Motilyn per milliliter.
PRODUCER: Abbott Laboratories, North Chicago.



• HYDROGEN FLAME DETECTOR

DESCRIPTION: This ultrasensitive accessory is designed to supplement the standard thermal conductivity detector used in the GC-2 Gas Chromatograph. It has a typical sensitivity of 50 parts per billion full-scale, and it is especially suited for detecting the presence of minute traces in complex organic compounds. The quick response and ultrasensitivity of this instrument permit operation with extremely small sample volumes. Included with the Hydrogen Flame Detector assembly are the electrometer, burner assembly, flow controls, mounting bracket and instructions for installation with the GC-2 Gas Chromatograph.
PRODUCER: Scientific and Process Instruments Division, Beckman Instruments, Inc., Fullerton, Calif.

• TOMAC INSTRUMENT TABLE

DESCRIPTION: Constructed of stainless steel, this instrument table has a tray which can be adjusted from 39¼ to 63¾ in. by a foot lever. The tray automatically locks in place and can be removed for autoclaving. The flat, double-pronged base allows ½ in. maximal clearance under all standard operating tables. The sleeve-type post design eliminates the danger of contaminated surfaces being exposed when the tray is raised.
PRODUCER: American Hospital Supply Corporation, Evanston, Ill.

• MAXIPEN®

PURPOSE: Antibiotic.
COMPOSITION: Alpha-phenoxyethyl penicillin potassium.
CAUTION: Contraindicated in patients allergic to penicillin.
DOSAGE AND ADMINISTRATION: For moderately severe conditions, 125 to 250 mg. three times daily; for more severe conditions, 500 mg. every four hours.
HOW SUPPLIED: Maxipen Tablets: 125 mg. tablets in bottles of 36; 250 mg. tablets in bottles of 24 and 100. Maxipen for Oral Solution: 60 cc. bottles of dry powder for reconstitution with water; each 5 cc. contains 125 mg. alpha-phenoxyethyl penicillin potassium.
PRODUCER: J. B. Roerig and Company, division of Chas. Pfizer & Co., Inc., New York.

(Continued on page A-134)

FREEDOM FROM ANGINAL ATTACKS

24 HOURS OF UNINTERRUPTED PROTECTION

WITH ONE TEMPULE®
MORNING AND NIGHT

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TEMPULES

controlled disintegration capsules

The best has been improved. PETN, proven over the years to be the most effective drug for preventing anginal attacks, has been improved by incorporating it into controlled disintegration capsules. Pentritol Tempules exhibit the benefits of PETN "...plus a smooth sustained clinical result that seemed to show a superior effect."[1]

Pentritol Tempules given every 12 hours reduced or eliminated nitroglycerin requirements, stopped anginal attacks or reduced their frequency, eliminated or mitigated pain, and increased the capacity for physical activity. *Patients previously taking PETN in tablets with little progress, responded favorably to Pentritol Tempules.*[2]

Recommended dose is 1 Pentritol Tempule morning and evening, approximately 12 hours apart. Available in bottles of 60 Tempules. Also available: Pentritol-B Tempules with 50 mg. of butabarbital added for vasodilation *plus* sedation.

1. Biegeleisen, H. I.: Clin. Med. 2:1005, 1955. 2. Roberts, J. T.: Clin. Med. 4:1375, 1957.

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• TOMAC STERISNAP NEEDLE PACK

DESCRIPTION: Constructed of plastic and moisture-resistant paper, this tray-type container provides individual sterile chambers for 20 hypodermic needles. Sterility is guaranteed by the specially designed chamber lip; unused needles remain sterile regardless of how many chambers are emptied. The chambers are shaped to support the cannulas so that the needle points do not touch the sides. The needle is removed by snapping the cap to expose the hub, which is fastened securely to the cannula. Each needle is color-coded according to gauge for identification.
PRODUCER: American Hospital Supply Corporation, Evanston, Ill.

• THIOSULFIL® FORTE
(New Dosage Form)

PURPOSE: To treat urinary tract infections.
COMPOSITION: Each tablet contains 0.5 gm. sulfamethizole.
PRODUCER: Ayerst Laboratories, Inc., New York.

• FOSTRIL® AND FOSTRIL HC®

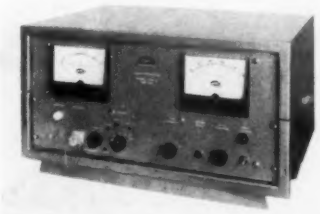
PURPOSE: To treat acne.
COMPOSITION: Fostril contains polyoxyethylene lauryl ether, sulfur, hexachlorophene and powder base. Fostril HC contains the same ingredients plus ¼ per cent hydrocortisone.
INDICATIONS FOR USE: Fostril is used in the average case of acne; Fostril HC is recommended in acne rosacea and in the presence of prominent inflammation and erythema.
DOSAGE AND ADMINISTRATION: One application daily; extremely oily skin may require a second application.
HOW SUPPLIED: Fostril, 1½ oz. tubes; Fostril HC, 25 gm. tubes.
PRODUCER: Westwood Pharmaceuticals, division of Foster-Milburn Company, Buffalo.

• SYNCILLIN® PEDIATRIC DROPS

PURPOSE: To treat penicillin-susceptible infections in infants and very young children.
COMPOSITION: In powder for solution. When reconstituted, each 0.6 cc. contains 125 mg. of potassium alpha-phenoxyethyl penicillin.
DOSAGE AND ADMINISTRATION: Orally, with dropper calibrated for 0.6 cc.
HOW SUPPLIED: 1.5 gm. of the antibiotic in 7.2 cc. bottles.
PRODUCER: Bristol Laboratories, Inc., Syracuse.

• HEPTUNA® PLUS
(New Formula)

PURPOSE: To treat microcytic and macrocytic anemias of nutritional origin.
COMPOSITION: Each 11 minim capsule contains six hematopoietic factors, seven vitamins and 10 minerals.
DOSAGE AND ADMINISTRATION: 1 or 2 capsules daily or as prescribed.
HOW SUPPLIED: Bottles of 100.
PRODUCER: J. B. Roerig and Company, division of Chas. Pfizer & Co., Inc., New York.



• LINEAR COUNT RATE METER
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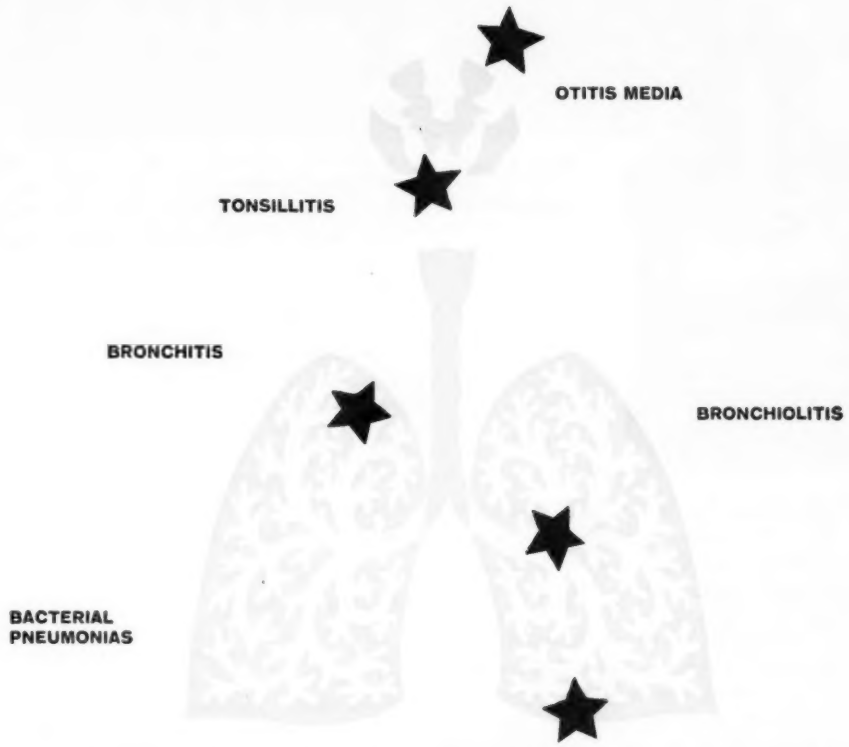
DESCRIPTION: Designed for measuring any function characterized by varying rates of flow, this instrument is ideal for studying blood circulation. With a Geiger-Müller, scintillation or proportional counter detector, diffusion of injected radioactive material may be traced and measured precisely. Six counting ranges and five time constants may be selected by panel control. A connector is provided for a graphic recorder. The unit measures 15½ by 20½ by 10 in.
PRODUCER: Nuclear Measurements Corporation, Indianapolis.

(Continued on page A-136)



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1. Lysaught, J. N., and Cleaver, W.: Proceedings of the Detroit Symposium on Antibacterial Therapy (Michigan and Wayne County Academies of General Practice, Detroit, Sept. 12, 1959).

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• THIN-WINDOW FLOW COUNTER (Model FCS-1)

DESCRIPTION: Designed for detecting and counting all types of ionizing radiation, this instrument is especially suitable for beta counting in the proportional region. Operating points are 2800 V for the alpha proportional region and 4000 V for the beta proportional region. Average plateau slopes are 2 per cent per 100 V for both alpha and beta plateau regions. Features include a cylindrical counting chamber with a 1 mil wire loop anode, covered by an aluminum-coated MYLAR® window less than 1 mg. per square centimeter in thickness, and a LUCITE® mount with five positions for a sliding source tray. A small bubbler mounted on the side of the instrument indicates gas flow rate.
PRODUCER: The Victoreen Instrument Company, Cleveland.

• TRYPP® NOSE DROPS

PURPOSE: Nasal decongestant.
COMPOSITION: Each 8 cc. contains 3 mg. (7500 units) trypsin and 20 mg. (0.25 per cent) phenylephrine hydrochloride with gelatin and other excipients and stabilizers.
DOSAGE AND ADMINISTRATION: For children, 1 to 2 drops in each nostril; for adults, 2 to 4 drops in each nostril. Repeat every three to four hours if necessary.
HOW SUPPLIED: Packages containing an envelope of powder and a dropper bottle of liquid diluent which makes an isotonic solution when mixed.
PRODUCER: U. S. Vitamin & Pharmaceutical Corp., New York.

• GERILIQUID

PURPOSE: Long-acting vasodilator and thermogenic agent.
COMPOSITION: Each teaspoonful (5 ml.) contains 75 mg. niacin and 750 mg. glycine in a sherry wine base. Alcoholic content is 5 per cent.
DOSAGE AND ADMINISTRATION: 1 to 2 teaspoonfuls three times a day before meals. The dosage may be reduced if objectionable flushing occurs.
HOW SUPPLIED: 8 oz. bottles.
PRODUCER: Lakeside Laboratories, Milwaukee.

• STREP-DISTRYCILLIN A.S.

PURPOSE: Antibiotic.
COMPOSITION: Streptomycin suspended in an aqueous solution.
HOW SUPPLIED: 2 cc. and 10 cc. vials.
PRODUCER: E. R. Squibb & Sons, division of Olin Mathieson Chemical Corporation, New York.

• CLEANSING AGENTS

PURPOSE: To clean and sterilize surgical and dental instruments and sterilization equipment.
DESCRIPTION: Germicidal Concentrate: Used in cold sterilization of surgical and dental instruments, this agent contains benzalkonium chloride and will not damage instruments with aluminum parts. The recommended strength is 5 cc. of concentrate to 1 pt. of water.
Rinse: To prevent rust damage during the rinse cycle in washing instruments, 1 tablespoon of this mixture is added to 5 gal. of water. This agent is compatible with all soaps and detergents and also may be added to wash water.
Vapor Phase Rust Inhibitor: This preparation prevents rusting or oxidation of all metals, including carbon steel. It is sprayed on the wrappers covering clean instruments, and the package is then autoclaved. If instruments are stored for long periods, the wrappers may be sprayed once or twice a month.
Decalcifier: To remove solids deposited by water in hot-water sterilizers, vaporizers and autoclaves, ½ to 1 vial (32 gm.) of this decalcifying agent is added to 1 pt. of hot water.
HOW SUPPLIED: Germicidal Concentrate, 8 oz. plastic bottles; Rinse, 18 oz. cans; Vapor Phase Rust Inhibitor, 10 oz. plastic bottles; Decalcifier, 32 gm. vials.
PRODUCER: The Lorvic Corporation, St. Louis.

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MAY 1960

In Saving For A Child's Future College Education - can you use the so-called short-term trust for tax advantage? The short-term trust is one which is to continue for at least ten years. When the trust ends, the grantor gets his property back. During the term of the trust, income being accumulated belongs to the beneficiary and is taxed to the trust. Since the trust will be in a much lower tax bracket than the grantor, tax on trust income is minimized for greater savings. However, where a parent establishes such trust for a child, trust income will be taxed to the parent and not to the trust if trust income is used to discharge the parent's legal obligation to support the child.

Does a parent's support obligation to a child extend to education through college? Answer to that question depends upon operation of state law. The highest court in Mississippi recently ruled that a father whose economic circumstances permitted it was required to pay his daughter's college expenses. Apparently, similar rule exists in California, Iowa, Maine, Montana, New Hampshire, New York, Tennessee, Washington, and Wisconsin. In most other states, a father's support obligation for a child's college education is still unsettled. However, there is reason to believe that regardless of a father's wealth, he's not legally obligated to pay for a child's education in Pennsylvania and New Jersey.

The use of a short-term trust has been widely advocated as a means of conveniently saving for a child's college education - with tax advantages. Whether such advice is sound tax planning may well depend upon where the parent lives. Use of a short-term trust for a child's college education will not yield tax savings in some states, e.g., Mississippi.

When You Receive Dividends On Your Life Insurance - the dividends serve to reduce your premium costs. They are not taxable as income. That long has been the tax rule and it extends to cover all types of life insurance. A few years back, the Internal Revenue Service called the attention of veterans to such rule. A large number of ex-servicemen reported dividends on GI insurance

as taxable income. This coming year, an increased dividend on GI insurance is anticipated. The Internal Revenue Service has found it necessary to repeat its earlier instructions as to the tax treatment of dividends on GI insurance. Notwithstanding the earlier ruling, some veterans continued to report such dividends as taxable income.

* * * * *

Dollar Cost Averaging On Stock Purchases - is a long range investment plan. It is frequently advocated as a method of avoiding investment errors committed in attempting to catch market swings on purchases of stocks. Under dollar cost averaging, an investor invests a fixed amount regularly - monthly, quarterly, or annually. Since the same amount of money will buy more shares when prices are low than when they are high, the average cost of purchases will always be lower than the average price. Does the investment theory behind dollar cost averaging work out in practice?

Over the short-term, such systematic investing doesn't insure against market fluctuations. However, numerous studies indicate that over the long run, the averaging does yield investment benefits. A recent illustration assumed investment of $1,000 a year in stocks making up a widely used stock price index. Dividends on such investments were also reinvested. Initial investment was made back in 1929 shortly before the stock market crash - certainly not a propitious time for investment. Over a period, how did the investor fare out?

Three years after he started his investment program, he had invested a total of $3,070 which had a market value of a little more than $1,200. If the investor liquidated his investment then, he would have had a substantial loss. He continued his systematic investment through the depression 30's but it was not until 1943 that market value of his investments exceeded amount he had actually invested. However, thereafter the systematic investment program started to yield benefits in the form of sizeable appreciation. By 1949, his total investment of something less than $35,000 had a market value of close to $50,000. By 1959, his investments, including reinvested dividends, totaled some $90,000. If he liquidated such investment late last year, he would have received some $250,000 sales proceeds. After a capital gains tax of some $40,000, he would have netted cash proceeds of $210,000.

In Seeking Tax Protection On Dividends - from stock investment, you might check with your broker for companies which

have cash earnings in excess of taxable earnings. From time to time, some companies, as a result of favorable tax elections, are able to create such excess of cash over taxable income. That excess can be distributed tax free to stockholders. Some of these companies - although not all of them - qualify as growth companies as well. The companies which are able to declare tax-exempt dividends in whole or part number more than many investors realize. Sinclair-Murray, the publishing house which reports on capital changes, recently pointed out that in 1959 more than 300 publicly held companies paid these tax-sheltered cash dividends.

* * * * *

Is A Contract Surgeon With The U. S. Army - a member of the armed forces? A surgeon agreed during the term of an employment contract to perform the professional and administrative duties of an officer of the Medical Corps. Under his contract, the surgeon was entitled to the basic allowances for subsistence and quarters given members of the uniformed services. Such allowances, whether paid in kind or in cash, are not taxable to members of the armed forces. Does a contract surgeon benefit from similar tax exclusion? The Internal Revenue Service has now answered in the negative. The Service says that the contract surgeon is not a member of the uniformed services. As a result, subsistence and rental allowances paid him in cash must be reported as taxable income.

The Doctor Who Practices In Partnership - with other professional men now can secure pension benefits similar to those available to employes under a tax-favored employment plan. Such benefits are available to the doctor if he converts his partnership to an association taxable as a corporation. The Internal Revenue Service has so conceded. It also has issued proposed Regulations containing standards which must be met if the former partnership is to be recognized as an association.

However, the medical practitioner seeking tax-protected pension benefits by conversion of his partnership to an association will have to proceed slowly. The Internal Revenue Service has stated that the standards which must be met for an association are established by Federal law. However, in determining whether the legal relationship between members of a medical organization meets those standards is a matter of local law. And local law may vary considerably. It is quite possible that legal steps taken by one medical partnership might convert the partnership to an association in one state yet identical steps taken by another medical partnership in another state might not.

The Internal Revenue Service is being urged to drop this local law test when it issues final Regulations on conversion of a medical partnership to a medical association. However, unless it does, state law, as well as Federal law, will have important application to medical men seeking pension benefits under a medical association.

* * * * *

Joint Ownership Of Property By Husband And Wife - may offer advantages. For instance, under state law, it may facilitate probate proceedings and administration of an estate on death of one of the joint owners. However, a husband and wife considering putting property in joint ownership should proceed slowly - and only with the advice of legal counsel. Joint ownership can have disadvantages, too.

A professional man with substantial income gave all his stocks to his wife. He retained other income-producing property in his own name, e.g., real estate investments. Some ten years later, the couple decided to put all property holdings in their joint names. The wife transferred the securities which her husband had previously given to her into joint ownership. Still later, the husband died.

While under state law, jointly held property may not be part of the decedent's probate estate, such jointly held property is part of a decedent's Federal taxable estate to the extent that his funds were used to purchase it. Here, only the husband's funds had been used in purchasing security holdings of the couple. Thus, all stocks and bonds held in the couple's joint name were subject to tax in his estate.

If the wife had retained separate ownership of the securities in her name, the estate tax on such securities on husband's death would have been avoided. That would have been the result even though such securities were originally purchased with the husband's separate funds.

* * * * *

Deduction For Postgraduate Study - has been further clarified under a new ruling. While directed primarily toward the schoolteacher, it could have important consequences to self-employed professional man. The time and money spent on additional education doesn't determine deduction. For example, a schoolteacher takes an additional year's education to maintain or to improve skills in present job. Deduction is allowed. But if same courses allowed advancement to a better position, expenses could not be deducted.

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► DIAGNOSIS AND TREATMENT OF TUMORS OF THE CHEST

Edited by David M. Spain, M.D., Associate Professor of Pathology, Columbia University College of Physicians and Surgeons, New York, with 26 contributors. 371 pages, illustrated. 1960, Grune & Stratton, Inc., New York and London. $14.75.

The American College of Chest Physicians, which sponsored this book, may be justly proud of the excellent work of the editor in compiling a complete and authoritative coverage of the field of chest tumors by outstanding contributors. Recent progress in the diagnosis and treatment of chest diseases has been so rapid that subspecialties in this field already have arisen. The material presented in this book represents the specialized experience of a group of authors, and it is the very latest information available.

The first nine chapters include a number of specific and general aspects of lung cancer and cover the etiology; pathogenesis; pathology; medical, cytologic and roentgenographic diagnosis; and treatment of this disease. The material is excellently arranged, providing continuity of thought with no unnecessary overlap, as is frequently the case when multiple contributors present individual views. The authoritative coverage of various sections is apparent when one sees that the contributors are men such as Dr. Arthur Purdy Stout, who wrote on pathogenesis of lung cancer, and Dr. Leo G. Rigler, who discussed roentgenographic diagnosis.

The remaining 10 chapters cover the various forms of tumors by types and by anatomic location. All intrathoracic tumors, including tumors of the thoracic wall, diaphragm, esophagus, heart and pericardium and metastatic tumors, are discussed in addition to the tumors of the mediastinum and pulmonary parenchyma. The last two chapters are devoted to radiation and isotope therapy and to treatment of inoperable primary tumors of the chest. The material presented includes key statistical studies with data to substantiate the various conclusions reached by the authors.

Y. S.

► CURRENT THERAPY 1960

Edited by Howard F. Conn, M.D., with 12 consulting editors. 808 pages. 1960, W. B. Saunders Company, Philadelphia and London. $12.00.

As in the past editions, the new edition of this book presents up-to-date methods of treating most of the diseases encountered by the practicing physician. Most of the therapeutic methods have been rewritten by new authors or have been revised. Some disease entities have been omitted from the text and others have been added.

One of the most unusual treatments is that proposed by Walter L. Bloom for obese patients whose condition has been refractory to other regimens. It is a method consisting primarily of fasting the patient for four to nine days in the hospital before prescribing a diet of 600 to 800 calories for him. It will be interesting to see how effective this treatment will be in selected patients.

In view of the rapid changes in therapy that are constantly taking place, the practicing physician must have access to an up-to-date text on treatment. This book fills this need.

R. V. R.

(Continued on page A-172)

► THE YEAR BOOK OF DRUG THERAPY (1959-1960)

Edited by Harry Beckman, M.D., Director, Departments of Pharmacology, Marquette University Schools of Medicine and Dentistry, Milwaukee. 570 pages, illustrated. 1960, The Year Book Publishers, Inc., Chicago. $8.50.

Dr. Beckman has added an excellent section to this volume, which includes a note to the reader on drug advertising, the bases for judgment of a new drug, and a list of the year's new drugs. This very fine section is followed by a discussion of the various drugs.

This is an excellent volume and I recommend it highly to all practicing physicians. The message to the reader is propounded with Dr. Beckman's usual courage in matters pertaining to the whole of medicine and is well worth the price of the volume.

I. P. F.

► CLINICAL PROSTHETICS FOR PHYSICIANS AND THERAPISTS

By Miles H. Anderson, Ed.D., Director, Prosthetics Education Project, Charles O. Bechtol, M.D., Professor of Surgery (Orthopedics), and Raymond E. Sollars, Associate Director, Prosthetics Education Project, University of California at Los Angeles School of Medicine. 393 pages, illustrated. 1959, Charles C Thomas, Springfield, Illinois. $10.50.

A real gap in the field has been filled very well by this new volume on the clinical practice of prosthetics. At long last those involved in prosthetics have a sound guide that is not forbidding in length or technology.

Prosthetics for both the upper and lower extremities are covered in two sections for both unilateral and bilateral amputees. The authors explain the necessity for, composition and operation of a clinic team in the total rehabilitation of amputees. The psychologic aspects of the problem, an understanding of which may often mean the difference between success and failure, are also considered.

There are many helpful suggestions for the physician regarding preoperative and postsurgical care, components, prescription, prescription philosophy, and check-out.

The therapist will find excellent chapters devoted to the training of amputees both in regard to stump strength and range of motion and in the use of the prosthesis.

The discussion of components might have been better placed at the beginning of each section, since the rest of the text might then have been more easily followed. Further, there is insufficient detail on the components, such as hooks, elbow units, etc.

Aside from these minor flaws, however, the book will prove a boon to clinic teams working with amputees.

J. S.

► THE MEGALOBLASTIC ANEMIAS

Modern Medical Monographs. By Victor Herbert, M.D., Instructor in Medicine, Harvard Medical School, Boston. No. 18. 162 pages, illustrated. 1959, Grune & Stratton, Inc., New York and London. $6.00.

Although this is a short monograph, it contains a concise, up-to-date review of the literature pertaining to the megaloblastic anemias. This is supplemented by the author's personal experience with more than 200 cases.

At first glance, important aspects of these anemias appear to have been minimized; for example, only three pages are devoted to the biochemical basis of megaloblastic hematopoiesis. In the section dealing with the clinical picture in these deficiency states, an unbalanced emphasis apparently has been placed on the neurologic complications in comparison to that accorded the rest of the symptoms. However, there is a complete bibliography with frequent and pertinent references throughout the text. It is, therefore, clear that the author's intent was not to cover the subject completely, but to present a very readable, concise monograph on the more important aspects of his topic. This policy makes the book more appealing to a larger group of readers; it also is valuable to the hematologist.

A few of the tests referred to in the section on laboratory evaluation of these anemias are not defined clearly enough for the average reader. A few more lines describing the technic of these tests would have been desirable before the presentation of the entirely reliable criticism of the available laboratory procedures.

R. W. H.

(Continued on page A-174)

while she is planning
her family,

**she needs your help
more than ever**

the most widely prescribed contraceptive

Ortho

WHENEVER A DIAPHRAGM IS INDICATED

► THE YEAR BOOK OF OBSTETRICS AND GYNECOLOGY (1959-1960)

Edited by J. P. Greenhill, M.D., Professor of Gynecology, Cook County Graduate School of Medicine, Chicago. 573 pages with 27 illustrations. 1959, The Year Book Publishers, Inc., Chicago. $8.00.

To the general practitioner, as well as the specialist, this text offers a capsule version of the most timely topics and opinions appearing in the world literature on obstetrics and gynecology. In addition, the editor presents in selected areas his comprehensive views based on years of experience in this field.

Selected subjects for review which normally would not have appeared in abbreviated form have been added to this edition. These include a review of the conference on the uterus, held by the New York Academy of Sciences, and abstracts from presidential addresses delivered by acknowledged leaders before their respective societies.

This volume will serve as a ready reference and its accompanying quiz will provide a mental stimulant.

E. A. B.

► DISEASES OF THE CHEST, INCLUDING THE HEART

Edited by J. Arthur Myers, M.D., Professor of Internal Medicine and Public Health, University of Minnesota Medical, Public Health and Graduate Schools, Minneapolis, with 34 contributors. 1,015 pages, illustrated. 1959, Charles C Thomas, Springfield, Illinois. $34.50.

Dealing with diseases of the chest and including, almost as an afterthought, the heart, this volume has an imposing bulk and an excellent list of contributors. In general, it is a good book but rather expensive for the average bookshelf.

Perhaps the main fault in this text is that in this day of superspecialization an attempt is made to cover too many aspects of this field. Thus, the cardiologist may find minor faults and omissions in the second half of the book, and the specialist in thoracic disease may note similar defects in the first half. For example, undue emphasis is placed on bronchopulmonary moniliasis as a primary disease, while no mention is made of esophageal motility studies or of farmer's lung. Furthermore, there is no reference to the use of dye curves in cardiac catheterization.

For the clinician, however, this is a good, sound book, written in a straightforward manner and well supplied with lists of recent references. It is conservative and authoritative. It sets out to do a great deal and succeeds in doing the major part of it very well.

M. B. D.

► PHYSIOLOGY OF THE EYE Clinical Application

By Francis Heed Adler, M.D., William F. Norris and George E. de Schweinitz Professor of Ophthalmology, University of Pennsylvania School of Medicine, Philadelphia. Ed. 3. 790 pages with 372 illustrations. 1959, The C. V. Mosby Company, St. Louis. $16.00.

A standard medical textbook used in most schools and hospitals since the first edition appeared in 1950, this work is a comprehensive and reliable repository of experimental and clinical data on one of the rapidly progressing fields of science in the medical curriculum. The arrangement of subject matter in chapters is based on anatomic areas and related functions. The commentary on laboratory findings and the evaluation of clinical observations that appear on each subject guide the reader in understanding some unusual and unfamiliar trends in interpreting the application of new theories.

Changes in our conceptions of the aqueous are rapidly reflected in the treatment of glaucoma as well as in responses to therapy for uveal disease. Tonography and tonometry have contributed to clinical diagnosis and treatment of glaucoma, and the current literature is replete with reported cases that refute, confuse or confirm conclusions of others. The deliberative consideration of the present status of research and of the examination of patients in this text is a welcome relief to the pangs of uncertainty that beset the casual reader.

The chapters on ocular motility and accommodation are classic examples of the author's preeminence in these subjects, and nothing in these fields seems to have been omitted in the present edition. Although electromyography and electroretinography are relatively new and unfamiliar topics, they are reasonably covered.

W. L. B.

(Continued on page A-176)

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► LECTURES ON THE INTERPRETATION OF PAIN IN ORTHOPEDIC PRACTICE

By Arthur Steindler, M.D., Professor Emeritus of Orthopedic Surgery, State University of Iowa College of Medicine, Iowa City. 733 pages, illustrated. 1959, Charles C Thomas, Springfield, Illinois. $18.50.

In this his last outstanding contribution to the field of orthopedic literature, the author has written a volume that is destined to rate among his greatest efforts. He has endeavored to analyze the manifestation of pain in relation to specific orthopedic conditions. Realizing that the symptom of discomfort is often the chief reason that a patient consults a physician, he has endeavored to establish the interrelationship of pain to various disorders of the musculoskeletal system.

Of the three basic manifestations of orthopedic disorder, which are deformity, dysfunction and pain, the last-mentioned symptom is often the initial complaint of the patient and is without question the least understood by the orthopedic surgeon. Pain as a symptom cannot be measured in units; however, there are certain qualities such as duration, intensity, recurrence, localization and referred discomfort that tend to make available important information to assist in establishing a diagnosis. There is no simple answer to the question of pain as a presenting complaint. Although this is recognized by the author, he pleads for consideration of this complaint before the patient is sent to a psychiatrist to determine if the symptom is organic or functional.

The text is presented in lecture form, beginning with a general introduction to the perception and other aspects of pain. The discussion then extends to include various systems and finally a regional analysis of this symptom of pain. The technic utilized by the author in presenting his concepts is one of detailed anatomic direction, and it does much to kindle our appreciation for the many diagnostic problems that are encountered. Readers will tend to regard this book more highly than others chiefly because of the author's contributions to a little understood but basic feature of diagnosis.

Completed during the last days of his life, when the author himself was in severe terminal pain, the monograph is fundamentally important to the practice of medical diagnosis. It is a distinct privilege to have available a volume of this magnitude. It will serve as a basis for many objective symptomatic evaluations in the future. Every orthopedic surgeon and, indeed, every student of medical diagnosis should have access to this advance in the field of diagnosis.

E. H. O'P.

► PRINCIPLES OF DISABILITY EVALUATION

By Wilmer Cauthorn Smith, M.D., Chief Medical Advisor, Oregon State Industrial Accident Commission, Salem. 210 pages. 1959, J. B. Lippincott Company, Philadelphia and Montreal. $7.00.

The author has written a good guide for physicians involved in disability evaluation, as it is now practiced. He has attempted to "present and elaborate the philosophy and logic which must necessarily underlie any rational understanding of disability," and has made a valuable contribution to the understanding of the present-day, generally accepted concept of disability evaluation.

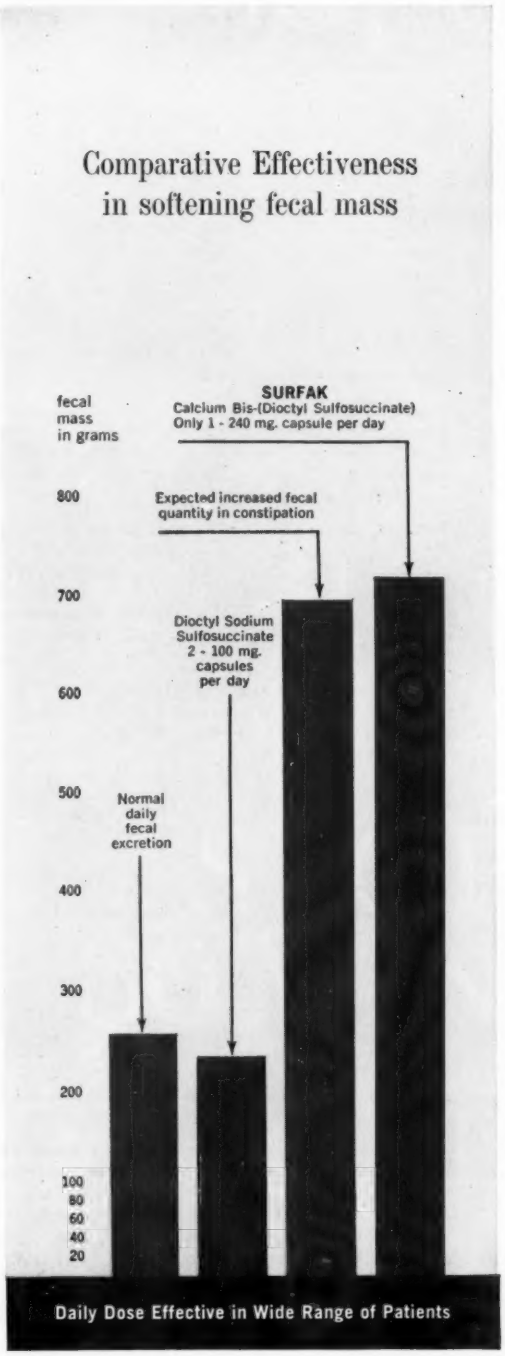
For this purpose, he has approached the problem by dividing the field into four general areas. The basic philosophy of compensation for disability, the need for valid evaluation of disability, and the natural obligation of the physician in the field of disability advice are covered in the first section. Practical suggestions are made for the writing of medical reports, testimony, and behavior on the witness stand.

In later sections, the nature of disability, relationship, and specific types of disability evaluation are discussed. Dr. Smith correctly points out that disability must be evaluated in terms of the person's ability to work. Evaluation of partial and total disability hinges on the person's ability or inability to engage in gainful employment. The section on relationship makes quite clear the necessity for establishing cause and effect and discusses the knotty problem of pre-existing conditions and aggravation following claim closure. Finally, the evaluation of specific areas of disability is discussed and general conditions are used to illustrate the mechanisms of evaluation.

This book certainly should prove useful to physicians in the field. However, some discussion of the growing tendency to evaluate disability in terms of total function rather than in separate "radicles" of the body would have added interest.

J. S.

(Continued on page A-178)



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► THE EXTREMITIES

By Daniel P. Quiring, Ph.D., Late Head of the Anatomy Division, Cleveland Clinic Foundation, Cleveland. Edited by John H. Warfel, Ph.D., Assistant Professor of Anatomy, The University of Buffalo School of Medicine, Buffalo. Ed. 2. 120 pages with 106 illustrations. 1960, Lea & Febiger, Philadelphia. $3.25.

The objective of this monograph is to provide a concise, handy aid to the study of the skeletal muscles of the human body, with clear and succinct demonstrations of their relationships with neighboring structures. The present edition was produced because of changes that were made in the basic texts used as references: "Gray's Anatomy" and Cunningham's "Textbook of Anatomy." The names of some of the muscles used in the first edition of this book have been changed to conform to the new nomenclature developed in Paris in 1955. Moreover, 14 plates from the first edition have been redrawn to correct some obvious anatomic errors which had impaired the originals.

For the young surgeon who does surgery of the extremities, for the anatomist, and for anyone else interested in the extremities, this book is worthwhile. It is briefly but adequately annotated, and the drawings are of exceptional quality, particularly from the standpoint of clarity.

E. W. J.

Books received are acknowledged in this department. As space permits, books of principal interest to our readers will be reviewed more extensively. Additional listings will be found on page 652 of this issue.

Handbook of Neurological Diagnostic Methods. Edited by Fletcher McDowell, M.D., Assistant Professor of Medicine (Neurology), and Harold G. Wolff, M.D., Anne Parrish Titzell Professor of Medicine (Neurology), Cornell University Medical College, New York. 201 pages, illustrated. 1960, The Williams & Wilkins Company, Baltimore. $4.50.

Dr. Schmidt's Baby Name Finder. By J. E. Schmidt, M.D., Chairman, National Association on Standard Medical Vocabulary. 390 pages, illustrated. 1960, Charles C Thomas, Springfield, Illinois. $10.50.

Anatomy; a Regional Study of Human Structure. By Ernest Gardner, M.D., and Ronan O'Rahilly, M.D., Wayne State University College of Medicine, Detroit, and Donald J. Gray, Ph.D., Stanford University School of Medicine, San Francisco. 999 pages, illustrated. 1960, W. B. Saunders Company, Philadelphia and London. $15.00.

An Atlas of Neurosurgical Techniques. By James I. Poppen, M.D., Neurosurgeon, Lahey Clinic, Boston. 522 pages, illustrated. 1960, W. B. Saunders Company, Philadelphia and London. $28.00.

Primary Tumors of the Calvaria; With Special Consideration of the Clinical Problems. By Franklin Jelsma, M.D., Assistant Professor of Neurosurgery, University of Louisville School of Medicine, Louisville. 116 pages, illustrated. 1960, Charles C Thomas, Springfield, Illinois. $7.00.

Surgery in World War II. Series on history of Medical Department, U. S. Army, in World War II. Neurosurgery. Edited by R. Glen Spurling, M.D., Professor of Neurosurgery, University of Louisville School of Medicine, Louisville, and Barnes Woodhall, M.D., Professor of Neurosurgery, Duke University School of Medicine, Durham, North Carolina, with 20 contributors. Vol. II. 705 pages, illustrated. 1959, U. S. Government Printing Office, Washington, D. C. $7.00.

Cosmetic Surgery; Principles and Practice. By Samuel Fomon, M.D., Director of Plastic Surgery, Manhattan General Hospital, New York. 651 pages with 608 illustrations. 1960, J. B. Lippincott Company, Philadelphia and Montreal. $27.50.

Enzymes in Health and Disease. Edited by David M. Greenberg, Ph.D., Professor of Biochemistry and Chairman of the Department, and Harold A. Harper, Ph.D., Professor of Biochemistry, University of California School of Medicine, San Francisco, with 26 contributors. 450 pages, illustrated. 1960, Charles C Thomas, Springfield, Illinois. $14.50.

Xylocaine; the Pharmacological Basis of Its Clinical Use. Edited by Sten Wiedling, Research Laboratories of Ab Astra, Södertälje, Sweden. 146 pages, illustrated. 1960, Almqvist & Wiksell, Stockholm, Sweden. English editions available from Astra Pharmaceutical Products, Inc., 7 Neponset Street, Worcester 6, Massachusetts.

Oxygen Supply to the Human Fetus. A symposium organized by the Council for International Organizations of Medical Sciences and the Josiah Macy Jr. Foundation, December 1957. Edited by James Walker, M.D. and Alec C. Turnbull, M.D., Department of Obstetrics and Gynecology, University of St. Andrews Conjoint Medical School, St. Andrews and Dundee, Scotland, with 21 participants. 313 pages, illustrated. 1960, Charles C Thomas, Springfield, Illinois. $10.50.

Cancer of the Cervix; Diagnosis of Early Forms. Ciba Foundation Study Group. Edited by G. E. W. Wolstenholme, O.B.E., and Maeve O'Connor, B.A. No. 3. 114 pages with 27 illustrations. 1960, Little, Brown & Company, Boston. $2.50.

Cardiac Auscultation; Including Audio-Visual Principles. By J. Scott Butterworth, M.D., Associate Professor of Medicine, Maurice R. Chassin, M.D., Associate Professor of Clinical Medicine, Robert McGrath, M.D., Associate Professor of Clinical Medicine, and Edmund H. Reppert, M.D., Assistant Professor of Clinical Medicine, New York University Post-Graduate Medical School, New York. Ed. 2. 102 pages with 68 illustrations. 1960, Grune & Stratton, Inc., New York and London. $6.25.

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MORRIS PLAINS, N.J.

PY-GP02

DR. Pepys' Pages

Personal Diary
and Observations on
Medical Life
by MORRIS FISHBEIN, M.D.

Mar. 1—In Phoenix at the Arizona Biltmore playing at golf and gin rummy and lost one game of "Scrabble" to Jean Lasdon. Reading now "Chautauqua," which has three authors but probably owes most to Dave Keene.

Mar. 2—To walk on the mountain and to sit by the pool gossiping with Max Schuster about forthcoming books. Then by the afternoon plane to Los Angeles, where Paul Wermer came to the airport, and to the Ambassador Hotel, where there was a reunion of alumni of the College of Medical Evangelists.

Mar. 3—Early awake and to visit the bookstores. In the afternoon came Mr. Harry Karl to present to the Institute for Advanced Learning in the Medical Sciences a check for $250,000, which old Pepys received. Thereafter a conference with all the leaders and found the whole occasion most interesting. Later to dine at Periono's, and then to hear the symphony.

Mar. 4—Early awake and out to Duarte to view the work at the City of Hope Medical Center. Here conferred with Ernest Beutler on new discoveries in hematology and learned much about his exciting research. Next to speak with Gene Roberts about the new discoveries in biochemistry of the brain and about L-glutamic acid. In the afternoon to walk the boulevards and to observe the changes taking place.

Mar. 5—Early to the airport and embarked for Denver. There sat in the airport some three hours reading "Hawaii," by James Michener. Then off on a DC-3 for Lincoln, arriving after more than a full day of travel.

Mar. 6—At noon to a brunch given by the officers of the Junior League. Then with Mistress Pepys for an interview on television, this being our first performance together. Thereafter to hear Vincent Price lecture on art, and talked with him about what turned out to be the favorite museum of both of us, the Prado in Madrid. In the evening to a great dinner at the Lincoln Country Club and met many old friends.

Mar. 7—Early came Dr. Fuenning of the Nebraska University Health Center, and with him made some tape recordings for use by the radio stations of Nebraska. Thereafter to speak at a convocation of the University of Nebraska on teen-age marriages and then to view the campus with all its new buildings and the library and many other fine facilities. Next to a luncheon attended by many hundreds and given under the auspices of the Junior League and the Executive Club. Here old Pepys spoke of the crisis in education, telling of the difficulties of our times and emphasizing particularly the need to begin learning a second language during the first year of school and also the importance of reading and reading and reading. Thereafter to a conference of the superintendents of the high schools of Lancaster County and in the evening to speak on the evolution of quackery at a fine dinner tendered by the Lancaster County Medical Society and its women's auxiliary.

Mar. 8—By the morning plane somewhat late to Chicago. Then all day at the desk working at the accumulated problems.

Mar. 9—To Roosevelt University and met with the heads of the departments of chemistry, physics and biology and talked with President Sparling about premedical education. After luncheon, again at the desk and in the evening to dine in the new restaurant which Citro has opened in the Shoreland Hotel.

Mar. 10—Again all day at the desk catching up with the columns for *McCall's* and with the editorials for POSTGRADUATE MEDICINE and the other writings that need to be done.

Mar. 11—All the morning at the desk striving to attend to many affairs. In the afternoon to the Chicago Symphony to hear John Barbirolli conduct Mozart and a symphony by Mahler.

Mar. 12—All this day reading and writing, and visited the Jackson Park Hospital. At night to the Standard Club to eat wild game shot by Theodore Vatz.

Mar. 13—Early awake and driving to Glencoe to speak at the North Shore Temple on the Jewish aspects of medical science. After the address, to luncheon with Justin and his fine family.

Mar. 14—To the headquarters of the American Dental Association for the Ninth Conference on Dental Journalism, which was perfectly arranged by Dr. Lon Morrey, president of the

(Continued on page A-192)

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American Association of Dental Editors. Here heard Theodore Van Dellen tell of the great improvements in prospect for the *Illinois Medical Journal* and reflect on the manner of its decline in recent years. Lunched with some 90 dental editors and their associates at the Pearson Hotel and spoke to them of the importance of professional journalism. Here Dr. Hillenbrand admirably executed a mass introduction of the 16 people at the speakers' table. Reading now Gerald Carson's "The Roguish World of Doctor Brinkley," which is a fascinating account of the world's greatest charlatan and his battle against the American Medical Association, the state medical organizations, the United States government, and Mrs. Brinkley.

Mar. 16—A great snow again pours down on Chicago. At noon to the Chicago Tuberculosis Institute's luncheon to speak on "The count down in medical science"; here medals were conferred on Jim Hutton and Jerome Head. All the leaders were present for a fine meeting arranged by Egdorf.

Mar. 17—By the early plane to New York. En route began John O'Hara's "Ourselves to Know" and scanned two paperbacks, which represent a sort of degradation of literature now that their publishers have begun to publish originals. To the Waldorf and then driving with Charles Haney to Montclair, New Jersey. First with James Moniz and Mrs. A. H. Skogsberg and Mrs. D. J. Horton to see the Montclair Community Hospital, which was begun in a frame house in 1923 and since improved with a new building. This was the first hospital to have a complete series of operating rooms insulated against sparks, and now $1 million is being raised for new rooms and facilities. To the home of Charles B. Sanders, where for cocktails came some hundred guests, including Drs. Block, Shaefer, Colton and many more. Then with President Partridge to a dinner for some 600 persons in the Upper Montclair State College, and from Morris Plains came Fleming, Whitney, Marsden and Mae Murray. So spoke to an enthusiastic audience and back to New York.

Mar. 18—All the morning with Marsden and Douglass on the problems of *World-Wide Abstracts* and in the afternoon discussing *Medical World News* with Max Geffen and Bill White. Later with Mark Soroko to eat Black Angus steaks and then to see Maureen Stapleton and a wonderful cast in Lillian Hellman's "Toys in the Attic."

Mar. 19—For a long walk from the Waldorf to Rockefeller Hospital and enjoyed some hours of conference with Tom Rivers. To see a French motion picture called "The Lovers," which has been barred from Chicago. At night to the home of Arthur and Hilda Master for dinner.

Mar. 20—To Max Geffen's for lunch with Paul Robinson and the children; met L. Silver for some editorial suggestions, and then played gin with Max, who beat me again. Thereafter to the Stork Club for dinner with Mayes.

Mar. 21—For breakfast came Stan Henwood to talk of our international congresses. Next to see Milton Runyon at Doubleday's along with Richard Whittemore, and we worked out an edition of the *Adviser* in Afrikaans. To lunch came Bill Shepherd of Metropolitan Life and Harold Diehl, talking of changes in medical education and public health. Then to see Lewis Gruber and H. B. Parmele at The P. Lorillard Company now celebrating its two hundredth anniversary and doing well indeed. Back to the Waldorf to see Nelson of Cook's, and with Mistress Pepys he has worked out a great schedule for travel to a half-dozen conferences this summer. Next came Mark Soroko and Rose, and then to see "Fiorello," a musical based on the life of Mayor La Guardia, full of timely humor and melody.

Mar. 22—At noon came Basil O'Connor to discuss the new research institute in the Far West and the international congresses. In the afternoon again with Bill White, and then came Paul Hoeber and Algernon Reese to discuss the new edition of the latter's famous book on tumors of the eye. Thereafter to the airport and back to Chicago, reading en route "Winter Cruise" by Malm.

Mar. 23—Most of this day reading and writing and even a little arithmetic. In the afternoon came Mrs. Carole Levy and Bob Dachman to begin plans for the City of Hope and its Institute for Advanced Learning in the Medical Sciences.

Mar. 24—To confer with Peskin on epilepsy and its problems and to dine at Citro's with our guests Oscar Getz, Larry Joselit, Ted Vatz and Carol Gibbs.

Mar. 25—To the Don McNeill broadcast, where came great numbers of questions and was particularly pleased to hear from a woman of Welland, Ontario, that each morning she reads the

(Continued on page A-194)

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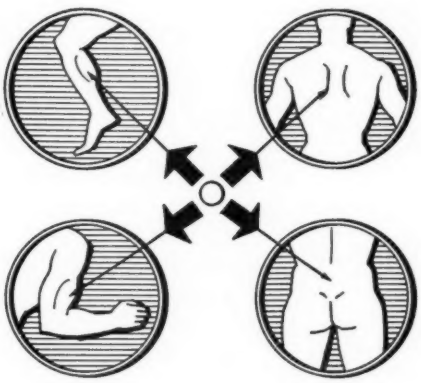

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INDICATED IN ALL TYPES OF ACUTE MUSCLE SPASM following sprains, strains, whiplash injuries, intervertebral disc syndrone, chronic osteoarthritis, etc.

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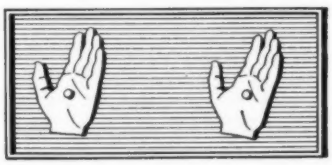

*Trademark U. S. Patent No. 2,567,351
Other patents pending

Riker
Northridge, California

creed for the aged which old Pepys wrote some time ago and published in POSTGRADUATE MEDICINE. At noon to the Covenant Club to plan the next "Salute to Medical Research."

Mar. 27—This day came Justin and Ann with the three children to Sunday brunch. Later saw the Boston Celtics demonstrate superiority over the St. Louis Hawks with a facility that almost surpassed the Globe Trotters. Reading also "Honor a Physician," by Philip Auld, which is a novelistic indictment of the British National Health Service that is more devastating than any of the learned economic texts that have been written about it. In the evening to the Hotel Hilton, where Mrs. Herman Jacobson, president of the Julian D. Levinson Foundation for the Mentally Retarded, presided and revealed how seven years of devotion to a cause brings great familiarity with its jargon. Dr. Capelitz told of recent research on the chromosomes which has improved our knowledge of mongolism, and old Pepys told of the rise of genetics to the very forefront of medical progress.

Mar. 29—Today came the announcement of the resignation of Larry Kimpton as the chancellor of the University of Chicago, and his loss to the University will be great, although reports say he will remain in the community. At noon came June Mantel and all the children for luncheon. Reading Shryock on "Medicine and Society in America, 1660-1860," the Phelps lectures of New York University. Reviewed this and "Speech and Brain Mechanisms," by Wilder Penfield and Lamar Roberts, which was given as the Vanuxem lectures at Princeton University. The latter should revolutionize the teaching of a second language to all our children.

Mar. 30—To meet with Dean Coggeshall, Mistress Pepys, M. Edward Davis and Sol DeLee to discuss the making of new educational obstetric motion pictures. In the evening to a dinner dance for the Jackson Park Hospital, where Barbara Friedell gave the grace and spoke for the women's auxiliary and M. T. Friedell and Gertz spoke for the staff.

Mar. 31—By the morning plane to Boston, flying around two hours over Buffalo trying to land, and finally after two failures making it. In Boston and driving with the Blodgetts to Brockton for a reception at the Brant Hotel; then to speak at the Armory to a thousand people in behalf of the Goddard Memorial Hospital at Stoughton.

RICHARD ARMOUR

QUICK SERVICE

Patients are impatient folk
Who will not wait to hear a joke
Or even pass the time of day,
But want their health back, right away.

They hate to sit there one full minute,
Mouth shut (thermometer jammed in it).
They can't bear waiting, not a bit,
For wounds to heal and bones to knit.

They want to be all well at once.
If you can't do it, you're a dunce.
And though they summon a physician,
They really need a good magician.

MURDER FOR LUNCH

Forensic scientists, if you please,
Were eating their lunch (M.D.s, Ph.D.s),
And meanwhile discussing criminalistics
Such as gunshot wounds, powder burns, ballistics.

One sketched on the tablecloth as he said,
"The slug went in here and came out of his head."
Another described, at the very first lull,
How a rapist had bludgeoned his victim's skull.

Two argued, with rival professional pride,
About arsenic versus cyanide. . . .
The talk was lively and gay and bright,
And all had a ravenous appetite.